Akademiya Nauk Uzbekskoi SSR
Institut Kraevoi Meditsiny

Ya. Kh. TURAKULOV

OBMEN IODA I TIREOIDNYE GORMONY

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АКАДЕМИЯ НАУК УЗБЕКСКОЙ ССР
ИНСТИТУТ КРАЕВОЙ МЕДИЦИНЫ

Я. Х. ТУРАКУЛОВ

ОБМЕН ЙОДА И ТИРЕОИДНЫЕ ГОРМОНЫ

ИЗДАТЕЛЬСТВО АКАДЕМИИ НАУК УЗБЕКСКОЙ ССР
ТАШКЕНТ—[illegible]

The Academy of Sciences of the Uzbek SSR

Institute of Endemic Medicine

Ya. Kh. TURAKULOV

THE METABOLISM OF IODINE AND THE THYROID HORMONES

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This book summarizes recent achievements in the study of the biochemistry of the thyroid gland hormones during the last 10-15 years. It gives an extensive survey of the scientific literature on the metabolism of iodine, and on the formation and metabolism of the thyroid hormones under normal and under pathological conditions of the thyroid gland. The work presents problems of the regulation of hormone production, the effect of various physical, chemical, and pharmacological factors on the processes of the absorption and metabolism of iodine. The action of radioactive iodine is examined in detail from the biochemical point of view.

The book also presents the results of research, obtained in the laboratory directed by the author, on the formation of thyroxin, the metabolism of iodine and thyroid hormones, in several forms of thyroid pathology.

This book is intended for scientific workers and endocrinologists who are interested in the physiology and the pathology of glands of internal secretion, especially in the thyroid hormones under normal conditions and in the presence of diseases of the thyroid gland.

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FOREWORD

During the last 20 years, our ideas concerning the physiology and biochemistry of the thyroid gland hormones have broadened considerably and have been corroborated by a series of fundamental discoveries.

The discovery of thyrostatic substances, which have found extensive therapeutic and experimental applications, was an important achivement leading to the clarification of the nature of the secretion of the thyroid gland, its interrelations with the anterior lobe of the pituitary, and also the direction of thyroid activity. Further discoveries in the fine mechanisms of hormone formation in the thyroid gland, the metabolism of thyroid hormones in the organism, and the effect of various internal and external factors on many aspects of thyroid functions are related to the use of the radioactive isotope of iodine—I^{131} as a tracer atom in clinical and biochemical research. The use of the method of paper chromatography and especially the combination of the chromatographic method with that of tracer atoms played no less a role in the attainment of the contemporary level of our knowledge in the field of biochemistry of the thyroid hormones. Thanks to the successful use of these two important methods, contemporary biochemistry succeeded in discovering new iodinated amino acids with hormonal activity, and in solving the problem of the nature of the iodinated components of the thyroid gland and of the circulating blood. This discovery has been the most important event in this field since the isolation of crystallized thyroxin by Kendall in 1915, its identification by Harington in 1926 and the synthesis of this hormone by Harington and Barger in 1927.

The results obtained in the study of the nature, the biosynthesis and the tissue metabolism of the thyroid hormones, starting from 1948, when monoiodotyrosine was discovered among the iodinated components of the thyroid gland, are the most outstanding pages in the history of the study of the biochemistry of hormones. Their importance permits their comparison with the period which began immediately after the discovery of thyroxin, opening a new era in the physiology of the thyroid gland.

Interest in the study of the biochemistry of hormones, and especially in the biochemistry of those of the thyroid gland, has considerably increased in scientific literature in relation to the important achievements in the study of these problems. But scientific literature existing on this subject in Russian is far from sufficient in order to meet the demands of wide circles of doctors and biologists. The list of books on the physiology and biochemistry of hormones, edited in the postwar years, is limited to only a few names /73, 96, 109/ while there are no monographs dedicated especially to the thyroid gland or to the biochemistry of its hormones.

This situation led us to summarize, to the best of our ability, the contemporary achievements of science in the study of the metabolism of iodine and of the formation and metabolism of the thyroid hormones. In this monograph, apart from a survey of the scientific literature, we present the results obtained in our laboratory on the metabolism of iodine and the thyroid hormones, under several forms of pathological conditions of the thyroid gland in humans; we also present material concerning several aspects of the metabolism during an experimental modification of the function of the thyroid gland in animals.

While compiling this monograph, we realized that one person could not hope to cope with the enormous amount of scientific literature on the thyroid gland. Thousands of new reports on the morphology, physiology and pathology of the thyroid gland appear annually. This is why we limited ourselves to presenting only basic works, most of which appeared during the last 8 to 10 years, on the biochemistry of the thyroid gland hormones. As to the clinical aspects of the above-mentioned problem, we reviewed only scientific literature on this aspect as much as was absolutely imperative for comparison with results of research performed in our laboratory.

The author leaves to the judgement of the scientific public the decision as to the extent to which all the basic achievements in the above-mentioned problems have been successfully summarized, and will be grateful for all the critical remarks that will follow about this work.

Ya. Turakulov

INTRODUCTION

The thyroid gland is one of the leading elements in the system of the glands of internal secretion. It holds an important position in the general hormonal balance of the organism and has a powerful regulating effect on its basic functions—growth, development, and metabolism. All the biological functions of the living organism are, doubtlessly, under the general control of the higher part of the nervous system and the endocrine glands are the major intermediate link in the realization of nervous action and effect it at the cellular level and in the intracellular structures, by way of emitting specific chemical agents—hormones. The activity of the thyroid gland itself is directly regulated by a hormone of the anterior lobe of the hypophysis cerebri—the pituitary, to whose directing control other glands of internal secretion are also subjected to a considerable extent. The hypophysis cerebri effects its regulating influence on the whole course of metabolism through the basic endocrine glands—by the secretion of various trophic hormones into the circulation—as well as through the direct action of its specific hormone—somatotropin—on the other organs and tissues. Thus, as an unknown author has so aptly put it, it may be said that, if the pituitary is considered as being the conductor in the endocrine orchestra, the role of first violin rightfully belongs to the thyroid gland.

The thyroid gland, as a basic organ for the metabolism of iodine, appears at a certain stage of the evolutionary development of the animal world. It exists in all vertebrates and in some chordates. It is possible that concentration of iodine also takes place in amphioxus and ascidians in a very primitive form.

The position of the thyroid gland varies in different animals. In humans, it has been classically described as a flattened bilobed pink structure weighing 25-30 g, situated on a level with the thyroid cartilage, at the sides of the larynx. The macroscopic aspect and the microscopic picture of the gland change considerably according to the age of the subject.

The thyroid gland has several functions in the metabolism of iodine in the organism. 1) it very actively concentrates iodide from the circulating blood and converts it into organically bound iodine, and into physiologically active specific hormones, 2) it serves as a reservoir for the thyroid hormones, which it fixes in the form of thyroglobulin and retains in its follicles, 3) it regulates the liberation of this reserved hormone under the constant and regulating control of the thyrotropic hormone of the pituitary, 4) it absorbs with considerable effectivity the iodine which is emitted during the metabolism of the thyroid hormones and retains it when the exogenous supply is insufficient.

The hormones of the thyroid gland have a maximal stimulating effect on intracellular oxidation of the whole organism.

According to contemporary opinion, the thyroid gland produces a series of physiologically active iodinated compounds, the main one being thyroxin. The basic physiological functions of the organism, as for instance heat production, i.e. the rate of metabolism, the growth and development of the whole organism, the metabolism of proteins, fats, carbohydrates, vitamins, many salts, and water are

under its control. The normal functioning of all the systems of the organism, its response to toxic substances, and its resistance to infections depend on the state of production of the thyroid hormones. The effect of thyroxin on metabolism lies undoubtedly at the root of all these reactions of the organism to the thyroid hormones. But, in the actual state of our knowledge on the mechanism of action of the thyroid hormones, we are still far from understanding the direct causes for the change of physiological functions of the organism, in response to the introduction of specific products of the thyroid gland.

Many questions of tissue metabolism and the peripheral action of the hormones of the thyroid gland still remain unclear, but considerable progress has already been achieved in the field of the basic problems of the biochemistry of this gland. Thanks to the successful use of the radioactive isotope of iodine — I^{131}, and the use of chromatographic analysis, we today have detailed information on the chemical interaction of iodine and the proteins of the gland in the formation of the iodinated amino acids – mono- and diiodotyrosine – and derivatives of thyronine which are active from the hormonal point of view. We know the composition of the thyroid hormones circulating in the blood, the tissue metabolism of thyroxin and other iodinated compounds, which are active from the hormonal point of view There are some assumptions, which are partly supported by experiments, on the nature of the active form of the thyroid hormones, having an immediate effect on the oxygen consumption at the cellular level. The scope of our knowledge of the mechanism of action of thyroxin has considerably widened, particularly during the last years. But there are still contradictory opinions on these important problems, which are intensively studied today.

The accomplishments of synthetic chemistry led to the acquirement of many structural analogues of thyroxin and to the clearing up of the question of the structural minimum for the appearance of a thyroxin-like action. The study of the chemistry and pharmacology of thyroid substances has disclosed the phenomenon of inhibition of the action of thyroid substances by antimetabolites, which are structurally related to them; these last evidently compete with the thyroid substances in their peripheral effect.

Particular importance is given to the problem of the mechanism of action of numerous pharmocological agents related to various classes of chemical compounds, having the capacity of blocking individual links in the intrathyroid metabolism of iodine. These agents, called antithyroid or thyrostatic substances, are capable of limiting the production of thyroid hormones; they have been extensively used in laboratory practice and in clinics for controlling hyperfunction of the gland.

Considerable disorders of iodine metabolism and the processes of hormone formation are observed in various forms of pathology of the thyroid gland.

The study of iodine and the thyroid hormone metabolism in various forms of thyroid pathology as well as in other diseases expanded very much since the first works applying radioactive iodine—I^{131}, in 1939-1940, indicating great prospects in the use of this isotope for functional research of the thyroid gland. In this case, as in other problems of endocrinology, clinical observations preceded experimental research.

If the reports of clinicians on the role of the thyroid gland, the causes of Basedow's disease and myxedemas, pushed chemists to take up the study of the composition of the thyroid gland which led to the isolation from it of biologically-active compounds, if the use of antithyroid preparations in the treatment of hyperthyroidism put before the experimenters the problem of clearing up the mechanism of their action, the use of radioiodine by clinicians for the evaluation of the functional state of the thyroid gland and for the study of the metabolism of iodine in

the organism opened wide vistas to biochemists, pathophysiologists, and other representatives of experimental science for comprehensive research into the formation, the transformation, and the metabolism of the thyroid hormones.

The experimenters brilliantly used this magnificent tool and obtained remarkable results in the discovery of many hidden aspects of the biochemistry of the thyroid hormones. The use of radioactive iodine in conjunction with the methods of chromatographic and electrophoretic analysis, which were elaborated somewhat later, led to the establishment of such new facts, which could not have been discovered by the methods of classical chemical analysis. We must particularly mention in this connection that experimental research in laboratories, on animals, was made simultaneously with clinical observations on humans and results obtained by the experimenters were often completed and confirmed by the clinicians. Such close cooperation was found to be extremely fruitful; it led to the speedy clearing up of many unsolved problems of the metabolism of iodine, especially in the presence of diseases of the thyroid gland. The final target of the experiments in this field is to correct disorders of the organism arising as the result of a pathological process or provoked by the researcher himself, taking into account the consistency and the mechanisms of development of the process. Considerable work has already been done by biochemists, but a further advance will depend on achievements in deciphering the mechanism of action of the thyroid hormones and the regulation of the function of the thyroid gland.

Research on the absorbtion of radioiodine by the thyroid gland, on the speed of the decontamination of plasma from I^{131} by the gland and the kidneys, on the emission of organically bound hormonal iodine, on the form of the binding of the iodinated compounds to blood proteins and their transportation in the organism, as well as the chromatographic identification of iodinated amino acids in blood and urine serve as clinical as well as laboratory tests for the functional state of the thyroid gland and constitute an important stage in the study of various forms of thyroid pathology.

[illegible] and pathology of the thyroid gland, the number of works in Russian literature on the biochemistry of the thyroid hormones is extremely scanty.

While further developing this subject, we will examine the biochemistry of the hormones of the thyroid gland under normal conditions and in the presence of some forms of thyroid pathology. As accepted in scientific literature, we shall examine consecutively the individual stages of iodine metabolism—the prethyroid, the intrathyroid and postthyroid stages. A series of questions having a physiological and pathophysiological nature, as for example the regulation of the thyroid hormone formation and secretion, the effect of thyroid gland hormones on various physiological functions and on the activity of the whole organism, the interrelation with other glands of internal secretion, the mechanism of action of antithyroid substances, are so closely related to the biochemistry of the thyroid hormones that it is not possible to evade them when discussing the biochemistry of the thyroid gland. It is also difficult to differentiate between the examination of the action and the transformation of the thyroid hormones in intact animals and healthy humans and between their effect in experimental thyroid pathology.

Our own material which includes [illegible] iodinated compounds i[illegible] during hypo- and hype[illegible] the proteins of the org[illegible]

animals (mice and rabbits). Results on the metabolism of iodine in the thyroid gland in thyroid pathology are related to patients suffering from various forms of goiter. Results of research performed by co-workers in the laboratory of biochemistry and endemic goiter of the Institute of Regional Medicine of the AS Uzbek SSR, which we directed, are also included in this book.

Chapter I

IODINE IN THE EXTERNAL ENVIRONMENT AND IN THE ORGANISM OF ANIMALS AND MAN

(Iod v okruzhayushchei srede i v organizme zhivotnykh i cheloveka)

1) The Distribution of Iodine in Nature and Inside the Organism

Our notions concerning the close ties between the thyroid gland and the metabolism of iodine in the organism obtained a firm foundation after successful research into the active principle of the thyroid gland, taken up in 1895/96 by the Freiburg chemist, Baumann (cit. from Trendelenburg, /142/), who discovered a very high content of this halogen in the composition of the gland.

Baumann became convinced that the iodine in the thyroid gland is firmly bound to the protein molecule, and he tried to isolate iodine-containing compounds by way of hydrolysing the proteins secreted by the tissue of this organ. But the merit of separating the iodinated protein which possesses hormonal activity goes to Oswald (cit.from Trendelenburg, /142/), who succeeded in isolating this protein, which he called thyroglobulin, by way of its precipitation from extracts of the thyroid gland with a semi-saturated solution of ammonium sulfate.

Thus, research into the hormonal principle of the thyroid gland confirmed previous guesses on the importance of iodine to the activity of the thyroid gland and gave a scientific explanation to the empirical methods of treating goiter by the administration of iodine-containing substances. From that time on, attempts to separate the most active preparations from the hydrolysates of the gland have been going on continuously At the same time, a great number of investigations have been made on the quantity of iodine in the gland of humans and various types of animals, depending on the age, the type of diet, the physiological state of the organism, the geographic conditions, etc

It was determined that the quantity of iodine in the thyroid gland of healthy persons and animals varies within considerable limits, depending on its content in the external environment: in the ground, air, and in alimentary products.

The daily demand of iodine of man and animals is, in all, 2-4 μg per one kg of weight, an average of 200 μg for an adult human /75, 106/. In places where there is no iodine deficiency in the ground, this demand is easily met with by the usual mixed diet.

Research on the quantity of iodine in water, ground, and alimentary products is extremely important, because of the role of iodine deficiency in the development of endemic goiter.

A great number of studies showed the existence of an inverse relationship between the quantity of iodine in the ground, water, and alimentary products and the

frequency of goiter among the population. According to contemporary notions, insufficient absorption of iodine into the organism has a leading role in the etiology of goiter. But the exogenous deficiency of iodine is not the only cause for endemic goiter. There are evidently also other exogenous and endogenous factors leading to the development of goiter in endemic centers, but they have not been precisely cleared up until now.

Problems of the etiology and pathogenesis of goiter are the center of attention of a great number of researchers, for the complete study of this problem has considerable theoretical interest and an important practical significance. The taking of extensive prophylactic measures for the total liquidation of goiter in endemic centers is also closely related to a correct understanding of the causes of the appearance and development of this disease.

The actual state of the question of the etiology and pathogenesis of goiter was brought to light in the monographs of O.V. Nikolaev /105/, B.V. Aleshin /8/, S.A. Masumov /93, 94/ and in a series of surveys /45/.

The global quantity of iodine in the human organism is, according to many authors, 20-30 mg, of which only 1/3 is found in the thyroid gland and the remaining quantity in all the other organs and tissues, without any particularly sharp differences in distribution per unit of body weight. The absolute quantity of iodine in the human thyroid gland reaches 10 mg. The endocrine glands contain relatively more iodine than other organs. Counting by percentages of iodine content, the thyroid gland is followed by the ovaries and the adrenal glands, but the ovaries accumulate iodine 70-100 times less than the thyroid gland and the adrenal glands even less than that. A considerable accumulation of iodine also takes place in some liquids of the organism. Thus, for example, the concentration of iodine in the salivary glands, in the gastric juices and in milk, is 40-50 times higher than its concentration in the plasma. Out of the total quantity of iodine in the organism, the greatest part is contained in the muscles, the skin and blood coming next, which is explained by their masses in the total weight of the organism. Thus, about one half of the total quantity of iodine is contained in the muscles, 3 mg in the skin and 8.5 ± 3.5 μg% in the plasma of healthy people.

Our notions concerning the distribution of iodine in the various tissues and organs of man are mostly based on the results of the quantitative determination of iodine in the organism of animals. There are only a few determinations of the distribution of iodine in the tissues and organs of man. In table I we show (for comparison) the distribution of iodine in the organism of man and rabbits. The results related to man are from the work of S.A. Masumov /93/, and those related to rabbits from the work of I.S. Izmailov /61/.

As may be seen from Table I, there are considerable differences between the results of the two authors, who have determined iodine by different methods. These differences concern first the liver, the kidneys, and the skin, in which I.S. Izmailov finds relatively small quantities of iodine. A series of other works show a high content of iodine in these organs and we tend to consider the results of the distribution of iodine in the human organism (Table I) as being in conformity with the truth. There is no basis for accepting any differences in iodine content in these organs of man and animals, though in experiments with radioiodine, only 0.0037 % of the administered tracer dose of I^{131} were found after eight hours in the liver of a rabbit /370/. The existing differences may be caused by errors of method, especially if the difficulty of determining small quantities of iodine in organs and tissues is taken into account.

The work of A.Z. Tsfasman and M.M. Petrova /163/, which shows the

distribution of I^{131} in the organs and tissues of a patient who died of Basedow's disease, has been published recently. Five days before her death, this patient was given 1.0 mC of radioiodine as a therapeutic. The results of the distribution of radioiodine in some organs of the patient are of certain interest (Table II).

Table I

The distribution of iodine in organs and tissues (in micrograms per entire organ)

Organs and tissues	Results of Istus 1924, subject: man	Results of Izmailov, 1942 subject: rabbit	Organs and tissues	Results of Istus 1924 subject: man	Results of Izmailov, 1942 subject, rabbit
Thyroid gland	9.760	2 651	Lungs	820	689
Blood	-	402	Brain	200	-
Spleen	560	436	Kidneys	1.053	91
Ovaries	413	-	Small intestine	119	-
Uterus	600	-	Pancreas	431	-
Testicles	500	1.065	Stomach	9.9	-
Adrenal Glands	636	69	Heart	-	702
Liver	1.224	66	Prostate	689	-
Skin	879	-	Adipose Tissue	0	-
Nails	800	-	Eyes	-	869
Lymph Gland	*600*	-	*Hair*	844	-

Table II

Content of I^{131} in various organs

Name of the organ	I^{131} in percentages of the *dose administered*
Thyroid gland	16.3
Liver	0.41
Lungs	0.18
Kidneys	0.15
Heart	0.14
Brain	0.05

Under normal conditions, there must evidently also be differences in the distribution of iodine in the organism and tissues of a rabbit and a man. In the above case, this difference in the distribution of iodine is aggravated by Basedow's disease, complicated by cardiac insufficiency, and cirrhosis, which caused a

considerable disorder in the metabolism of iodine. Nevertheless, the high content of radioiodine in the liver (0 41% of the administered dose), which is very close to the results of Table I, attract our attention .

2. Iodine Content of the Thyroid Gland

A considerable number of studies on the amount of iodine in the thyroid gland of various animals and of man were made since the works of Baumann. These determinations show, even in healthy organisms, considerable fluctuations of the iodine content in the thyroid gland depending on the type of animal, its age, the quality of the diet, and the geographic environment. A considerable number of works have also accumulated on the research of iodine in the thyroid gland of humans which has undergone pathological changes, in which results of basically the same order may be found, notwithstanding the presence of some considerable fluctuations in the obtained values.

Upon analyzing the results on the quantity of iodine, especially in other organs (other than the thyroid gland) where the iodine content is very small, the determination difficulties should be taken into account. There were a number of mistakes in the former methods in connection with that. A technique which was found to be reliable was that proposed by Fellenberg, based on the iodostarch reaction after alkaline hydrolysis, burning, aqueous and alcohol extractions, and oxidation with chlorine. As a result of the use of this method, proposed in 1926, many previous results on the iodine content of the thyroid gland were revised. But for the determination of hundredths of μg of iodine, i.e., a quantity contained in 1-2 ml of serum, the sensitivity of Fellenberg's method was found to be insufficient and this led to the use of a technique based on the catalytic action of iodine during oxidation of arsenous acid by certain salts (cerium-arsenic method). Many variants of this method are known at present, but they are all quite complicated and their execution demands great care and precision.

Therefore, the differences between the results obtained on the quantity of iodine in the thyroid gland, and especially in other organs and the blood, depend partly on the technique used. The results shown in Table I on the content of iodine in organs and in tissues were obtained by the old methods and are only tentative.

Iodine appears in the thyroid gland of animals at a very early age. The results of early research, using the classical methods of chemical analysis, as well as the new determinations employing radioactive iodine /102/, show that it appears at an early stage of embryonic development. A well-differentiated glandular structure develops in the human fetus by the 14th week and, at this time, the gland starts to concentrate iodine. Studies of cow embryos showed that their thyroid gland concentrates seven times more iodine than that of the mother, while the level of iodine in the blood of the fetus is lower than that of the mother's. A fixation of iodine on the tenth day was noted in chick embryos; the formation of active iodine—containing components already takes place during the second half of embryonic life during incubation. It is true that the embryonic thyroid gland and the gland of newborns always contains a markedly smaller quantity of iodine than the gland of adults. These results are shown in Table III.

According to the results of Baumann and others, the thyroid gland of children also contains less iodine than that of adults. A speedy increase of the quantity of iodine takes place later on, until the beginning of puberty; after this the rate of iodine increase in the thyroid gland decreases progressively. Results vary as to the content of iodine in the thyroid gland in advanced old age. Some authors point to a higher iodine content in old people; much information exists at the same time on the decrease of iodine in the thyroid gland in advanced old age.

Comprehensive research on the iodine content in the human thyroid gland was also made by Tsunts (cit. from Trendelenburg, /142/). According to his determinations, from 0.023 to 0.068% (an average of 0.056%) of iodine is contained in fresh glands of adults and an average of 0.229% with fluctuations from 0.119 to 0.286% in dessicated glands. According to these results, the iodine content of the whole gland fluctuated from 4.21 to 44.5 mg, with an average of 15 7 mg; these values are considerably higher than those obtained by other authors.

Table III

Changes of the iodine content of the thyroid gland of a human fetus and of children (from Trendelenburg, /142/)

Age	Total quantity of iodine in the thyroid gland, mg	mg% of iodine per wet weight of the gland
Human fetus aged 5 to 9 months	1-19	0.15-1.2 average 0.56
Newborn child	0.4-53	0.04-0.13 average 0.43
"	0.34	-
"	-	0.09-1.4 average 0.3
"	10.6-11.3	-
Stillborn	16-48	0.8-1.45 average 1.11
Newborn child	-	2.244-7.373 (according to Mayat and others, /95/)

Geographic conditions have considerable influence on the iodine content of the thyroid gland of humans as well as of animals. It was thus noted that the thyroid gland of Icelanders has a very high content (up to 0.083% of the fresh tissue) and this can probably be explained by the consumption of a great quantity of iodine in the food. An enormous quantity of iodine (up to 1.0% of the weight of the gland) was found in the thyroid gland of sheep grazing by the seaside.

Attention was also paid to perceptible seasonal fluctuations in the iodine content of the thyroid gland of some farm animals in various localities. The minimal iodine content of the gland was often found to be present during the spring months and the maximal one during the summer and autumn months. We have no definite knowledge of the causes of these seasonal fluctuations of iodine, but it can be assumed that they depend on changes in the iodine content of the animal's food in the different seasons of the year.

The average amount of iodine in the whole gland of an adult man is 6-9 mg. If we exclude extreme values the content, as percentage of the weight of fresh glands, is 0.056, that of the weight of the dessicated gland is 0.1-1.1 /484/.

The considerable fluctuations observed reflect, apart from the influence of geographic conditions and diet, big individual differences, which are determined by

many factors pertaining to the internal and external environments of the organism. When analyzing the iodine content of the thyroid gland of people living in localities where goiter is frequent and those of others living in areas where goiter does not occur, it was not possible to determine any clear cut consistency, although a number of authors note perceptibly lower values of iodine content of the glands of people living in endemic centers of goiter.

In the thyroid gland iodine is found in the colloid as well as inside the cells. Without entering upon the problem of the forms of iodine in the various morphological structures of the gland, and of the dynamics of iodine entry into the separate parts of the parenchyma, we note that, according to the results of many researchers, the main amount of iodine is present in the colloid. The coefficient of iodine in the cells as compared to the quantity of iodine in the colloid fluctuates considerably, and its average, in man, is 0.22 (cit. from Trendelenburg, /142/).

The iodine content of the thyroid gland during morphological changes was studied many times. Results obtained show important fluctuations of the iodine content, depending on the character of the goiter and the presence of degenerative or hyperplastic processes. But in view of the great individual fluctuations in the quantity of iodine which also occur in normal thyroid glands, it is only possible to speak of the direction of the change in iodine content in pathologically changed glands. During colloid goiter the increase in the quantity of colloid is accompanied by an increase of iodine content only during the first stages of the development of the goiter. As colloid accumulates in the goiter there is a cessation in the accumulation of iodine and its relative quantity becomes reduced. And in the presence of parenchymal goiters, which are poor in colloid, a considerable lowering of the iodine content is also noted. According to the early results of Marin and his co-workers (cit. from Trendelenburg, /142/), if the hyperplasia is more severe then the iodine content of the thyroid gland is lower.

Research work was made in our laboratory on the general iodine content of normal glands (of cadavers) and of pathologically changed glands, removed by operations /146/. In the presence of various forms of goiter iodine was determined separately on the tissues of the gland and on the colloid of the nodule. We found the iodine content of normal glands to be 14.7 to 70.5 mg% of the wet weight. The absolute quantity of iodine varied from 0.26 mg in a year-old child with a gland weighing 1.71 g, to 24.53 mg in an adult man with a gland weighing 34.8 g. In a gland modified by goiter the percentage of iodine was considerably lower (1.5-15.7 mg%), although its total quantity reached high values in view of considerable dimensions of the nodule or of the gland, which reached several hundreds of grams in a number of cases.

Problems of the metabolism of iodine under pathological conditions of the thyroid gland will be examined in greater detail in Chapter IX of this book.

Chapter II

THE PRETHYROIDAL METABOLISM OF IODINE

(Pretireoidnyl obmen ioda)

1. The Absorption of Iodine from the Gastrointestinal Tract and its Distribution in the Organism

The source of iodine for the thyroid gland is the iodine of the blood, which is continuously replenished, mainly due to its entry with food through the gastrointestinal tract and also, to a lesser degree, due to metabolic degradation in the tissues of the organic iodine of hormones which are synthesized in the gland.

The main part of the iodine entering the organism is in the form of iodide, which is very easily absorbed into the blood from the intestine. Other forms of iodine entering the intestine are converted into iodides before absorption. This process evidently takes place all along the gastrointestinal tract. Substances containing organic iodine, as for example iodinated fatty acids, diiodotyrosine and thyroxin, are also absorbed from the intestine. Occasional iodine-containing drugs may also serve as a source for the general iodine pool. Even painting the skin with iodine tincture leads to its absorption by the thyroid gland.

The speed of iodide absorption from the gastrointestinal tract is an exponential function of its quantity. The iodine compounds (iodinated fatty acids) are the most easily absorbed from the intestine, next come the inorganic salts (NaI, KI and others); organic iodine-containing substances such as thyroxin, diiodotyrosine, are also absorbed rather speedily in the intestine. It was established that about 5% of the iodine concentration present is absorbed by the blood every minute from the gastrointestinal tract. Iodine entering the blood through the portal vein may remain for a certain time in the liver, which has the faculty of regulating the passage of iodine into the blood circulation, preventing too sharp an increase of its quantity, in case iodine is contained in excessive amounts in the food.

Iodine entering the blood speedily disappears from it, the concentration of iodide in the blood at the moment of administration determines the speed of its absorption by the thyroid gland, its excretion in the urine, and its utilization by the various peripheral tissues.

The extent of distribution of iodides in man is about 40% of the body weight, but it takes at least five hours for total equilibrium to be established. The iodine ion is found in the plasma in very low concentrations—from 0.1μg to 0.5μg in 100 ml—and is distributed in a very specific manner between the plasma and the erythrocytes, approximately in the same manner as chlorides.

Even before the use of the radioactive isotope of iodine, the metabolism of iodide and of the iodine-containing compounds of the thyroid gland was widely studied in animals as well as in man. But early research could only be made upon

administering considerable quantities of thyroxin and diiodotyrosine, as it was then necessary to perform the determination of iodine by the classical methods of chemical analysis. But these studies always left in doubt the degree to which the results, obtained by means of considerable quantities of these compounds, reflect the endogenous metabolism of iodine under physiological conditions. The same study was repeated many times with the use of radioactive iodine. The fundamental assumption in this direction was that the distribution and metabolism of I^{131} reflect in full the real metabolism of all the iodine and consequently also that of the stable iodine in the organism.

One of the first studies in which I^{131} was employed was the research made by Perlman, Chaikoff and Morton /453/. These authors determined the distribution of iodine in all the organs of a rabbit (except the thyroid gland) at various intervals after the administration of tracer doses of radioiodine. The results of this research show that after the first interval after the administration of iodine, apart from the thyroid gland, the greatest quantity of iodine is to be found in the kidneys, through which the excretion of a considerable amount of iodine takes place. During the first 197 hours after the injection of iodine, its distribution in the organs undergoes considerable change; this is caused by the inclusion of a basic amount of I^{131} into the composition of the hormones of the thyroid gland, as well as by the characteristics of the distribution of organically bound iodine in the organism. The greatest loss of the initially absorbed iodine in the liver and muscles takes place during this period.

Thorough research on the distribution and metabolism of I^{131} in rats by the use of physiological quantities of radioactive iodine, diiodotyrosine and thyroxin, was performed by Johnson and Albert /370/. The rat received one ml of a solution containing 0.1 mg of sodium chloride with 0.5 μC of I^{131}. It was determined that the basic mass of the administered radioiodine becomes metabolized or excreted during the first 48 hours. This may be established by determining the activity in vivo. But it is known from the previous works of Albert and Keating /178/ that in the above interval of time the inorganic iodine becomes distributed and excreted in the same manner as iodide, without transformation into an organic compound, except for the processes taking place in the thyroid gland.

Upon administering iodine, its main part is excreted during the first 48 hours in the urine (75 8 %), the excretion in feces was very small, and constituted less than 3 %. Study of the distribution of iodine in the tissues showed that after administration of radioiodine only its concentration in the thyroid gland and in the gastrointestinal tract was higher than in the blood. I^{131} is found in perceptible quantities also in the testicles, spleen, pancreas, thyroid gland, cardiac muscle, striated muscles, adrenal glands and in the brain. But iodine appears in these organs only sporadically and in small quantities of no considerable importance. No accumulation of iodine was noticed in other organs.

[illegible] tract concentrates [illegible] ctivity was [illegible] Radioactivity [illegible] the gastrointestinal tract.

When feeding organic iodine it is absorbed much more slowly than iodide. Apart from this, the excretion of iodine in the feces (11-60 % of the administered dose) rises considerably.

In hypothyroidism there is decreased absorption from the gastrointestinal tract; and in hyperthyroidism too increased activity of the intestine limits absorption.

A short time after administration, a considerable part of the organic iodine (iodotyrosine, thyroglobulin) is converted into iodide. Soluble compounds like thyroxin are well absorbed, without deiodination. But soon after the absorption of the organic compounds from the gastrointestinal tract a progressive transformation of the bound iodine into iodide is observed in the blood.

There is nevertheless a considerable difference between the fate of diiodotyrosine and thyroxin. It was shown by the research of Johnson and Albert /370/, that upon administering physiological doses of labeled diiodotyrosine it is excreted from the organism and is distributed in the tissues similarly to the excretion and distribution of radioiodine. Diiodotyrosine is speedily deiodinated and I^{131}, entering into its molecule, appears in the form of radioactive iodide mainly in the urine. After administering radioactive l-thyroxin it remains in the organism for a considerably longer time and during 48 hours only 30% of the iodine of thyroxin is excreted in the urine and 40% in the feces. The radioiodine remaining in the organism is retained in the composition of the hormone.

Table IV

Distribution of I^{131} in various tissues and organs

Tissues and Organs	Percentage of the dose per one gram of tissue								
	Labeled iodide			Labeled diiodo-tyrosine			Labeled thyroxin		
	hours			hours			hours		
	3	6	24	3	6	24	3	6	24
Blood	2.9	2.5	0.4	1.5	1.3	0.5	1 2	0.8	0.3
Thyroid gland	76.9	73.0	163.9	17.7	20.2	85.2	-	-	-
Stomach	20.4	19.3	1 5	7.0	5.3	1.5	1.4	0.9	0.4
Contents of stomach	102.3	156.3	4.1	35.8	95.8	5.9	6.0	16 4	3.5
Small intestine	1.7	0.7	0.2	0.6	0 6	0.2	3.8	0.8	0.2
Contents of small intestine	12.0	9.2	0.7	3.5	3.3	1.0	145.8	29.7	1.0
Large intestine	1.5	0.7	0.3	0.3	0.4	0.2	0.8	0.9	0 3
Contents of large intestine	1.5	1.1	0.6	1.0	1.0	0.5	4.0	59.9	2.3
Liver	1.7	1.0	0.1	0.6	0.6	0 2	4.6	4.2	2.4
Pancreas	1.8	1.7	0.6	0.6	0.8	0.3	0.7	0.3	-
Salivary glands	1 8	1.5	0.5	0.6	0.5	0.3	0.8	0.3	-

The distribution of radioactivity in the organism of rats after the administration of physiological quantities of iodide, diiodotyrosine, and thyroxin is shown in Table IV, reproduced from the article by Johnson and Albert /370/.

After administration of most organic compounds of iodine inorganic as well as organic iodine appear in the blood. Organically bound iodine also appears in

the urine after administering thyroglobulin and considerable quantities of thyroxin (5-15% of all the iodine of urine). The organic fraction diminishes relatively with time and after 4 days it can no longer be discovered.

Keating and Albert /378/ studied the distribution and metabolism of thyroxin in patients suffering from thyroid pathology, after administering radioactive I^{131} labeled thyroxin Upon administering 100 μg of 1-thyroxin to hypothyroid patients, the authors could determine only 10% of the activity in the neck region. Even upon administering daily doses of 0.5 mg thyroxin, all the iodine was found by the third day to be protein-bound. But, when the patients became euthyroid, the whole tracer dose was in the form of iodide and its absorption in the neck was not noted. Urinary excretion rose from 69% before treatment to 78% after treatment. Upon administering I^{131}-thyroxin to healthy people it does not become taken up in the region of the neck, increase of the protein-bound iodine can be discovered soon after administration, and the excretion of iodide in the urine and feces is noted only considerably later.

2. Decontamination of Plasma from Iodine

In the first studies employing the radioactive isotope of iodine—I^{131}—it was already shown /341/ that, upon its administration to the human organism in physiological doses, the main part of the iodine is excreted in the urine within the first 24 hours, about 80% of iodine are excreted by healthy people during the first 48 hours, and its excretion falls off sharply during the following days. The removal of iodide from the iodine pool depends almost exclusively on its excretion in the urine and on its being organically bound in the thyroid gland. The speed of excretion and of binding are quite aptly determined as being kidney and thyroid gland clearance of iodide from the plasma. This notion was first introduced by Myant and his co-workers /435/, who, using tracer doses of I^{131}, expressed in the following form, that clearance is the ratio between the quantities of iodine removed by the thyroid gland from the plasma per unit of time.

$$\frac{\text{accumulation of iodine by the organ per unit of time}}{\text{concentration of iodide in the plasma}}$$

In healthy people, the decontamination of plasma from iodides by the thyroid gland went on at an average of 17 ml per minute, with fluctuations of 3-45 ml. In patients suffering from Basedow's disease the purification of the plasma took place considerably faster and fluctuated from 70 ml per minute to 1,000 ml and more. Research on the clearance of iodide from the plasma by the thyroid gland, made by A.Z. Tsfasman /161/, also showed 5-13 ml per min in normal cases. The rate of kidney clearance in healthy people was twice as high and averaged 35 ml.

In contrast to the clearance by the thyroid gland, which is very sensitive to fluctuations of the concentration of iodine in the blood, the kidney iodine clearance remained constant in all studies on the importance of iodine /241/.

A.Z. Tsfasman /162/ also determined the function of the thyroid gland after administering 1-2 μC of radioactive iodine, by measuring the excretion of I^{131} with the urine during 48 hours. Healthy people excreted 34-64% of the administered dose within 48 hours.

In this manner, the decontamination of the iodine pool is effected by the thyroid gland as well as by the kidneys and reaches in healthy people 50 ml of plasma per min, i.e., about 3 l per hour, from which the kidneys effect 2/3 and the thyroid gland 1/3.

Iodine clearance is subjected to considerable changes under pathological conditions. Hypophysectomy in rats considerably lowers the iodine clearance. A decrease of decontamination of plasma from iodides was also observed in people with myxedema and kidney diseases. The minute excretion of iodide through perspiration and exhalation has no perceptible effect on the decontamination of plasma from iodine contained in the blood.

Upon giving small doses of iodine about 80% is excreted in the urine and a very small dose with the feces. When administering considerable amounts the extent of the urinary excretion increases correspondingly. Thus, for instance, upon administration of 145 mg of iodine per day the urine contained 116 mg (75%), perspiration—24 mg and feces—5 mg.

A healthy person excretes in one hour 6% of the iodine reserve of his body; the rate of decontamination of the blood from iodine by the kidneys changes very little in the presence of various concentrations of it in the plasma. This leads to the assumption that iodine is usually passively absorbed by the renal tubules.

Thus, upon administering iodides their main mass leaves the organism within the first 24 hours. The remaining part of the iodides becomes mainly concentrated in the thyroid gland, but some other organs also have the faculty of accumulating iodine in perceptible quantities. Thus, for example, iodides are concentrated by the salivary glands, the stomach and the mammary glands. Their secretion was recently studied in detail on people by means of I^{131}. The following relationships of the concentration of iodine in these secretions to the iodine of the plasma were determined:

$$\frac{\text{I of saliva}}{\text{I of plasma}} = 40 \qquad \frac{\text{I of gastric juice}}{\text{I of plasma}} = 30$$

$$\frac{\text{I of milk}}{\text{I of plasma}} = 30$$

We may nevertheless state that the thyroid gland holds a particular position as to the trapping and storing of iodine, and that the quantity of iodine in the other organs, after the establishment of an equilibrium in the iodine pool, is insignificant compared to that in the thyroid gland.

Chapter III

THE METABOLISM OF IODINE IN THE THYROID GLAND

(mobmen iodavnutri shchitrovidnoi zhelezy)

The iodine cycle of the thyroid gland includes the following stages which occur consecutively fixation of iodine of the blood by the thyroid gland, its oxidation into elementary iodine, *biosynthesis of thyroid hormones and their accumulation in the* form of thyroglobulin, enzymatic hydrolysis of the protein with liberation of iodinated amino acids from the molecule of thyroglobulin, and finally, secretion of the prepared hormone into the blood circulation

We can only develop here the basic results of a great number of studies on each of the above-mentioned stages. But before we begin the examination of the intrathyroidal metabolism of iodine, it is expedient to bring forth the basic data on the chemical components of the thyroid gland.

1. The Chemical Components of the Thyroid Gland

The thyroid gland, as any other organ, is composed of proteins, fats, lipoids, carbohydrates, mineral substances, and vitamins. The hormonal secretion of the gland is related to the protein substance present in it, the particularity of which is the presence of considerable quantities of iodine in its composition.

Our first knowledge of this protein was obtained by Baumann in 1895-1896, when studying the active principle of the thyroid gland. His extremely important discovery on the constant existence of a firmly bound iodine compound in the gland laid the basis for further study, which has been going on until our day, on the chemistry and biochemistry of the iodinated compounds of the thyroid gland. Soon after the first works of Baumann the proteinic nature of this iodinated compound and its classification as a globulin was determined. Preparations of thyroidin or iodothyrin, obtained by Baumann by acid hydrolysis of the tissues of the thyroid gland, contained from 2.9 to 14.5% of iodine in their composition and were found to be, as he had supposed, iodine-containing products of the protein dissociation

The active iodoproteinic substance of the gland was isolated by Oswald by way of fractional ammonium sulfate precipitation of extracts of the thyroid gland and was named by him thyroglobulin or iodothyroglobulin. The quantity of this protein in the glands is very variable and amounts to 10-50% of the weight of the

Further research was directed to the separation of an active preparation of the hormone from thyroglobulin.

A great number of studies were begun with the use of various methods of

hydrolysis of thyroglobulin and of checking the activity of the preparations obtained until at last Kendall succeeded, in 1915, after many unsuccessful trials, in isolating a single chemical substance possessing the hormonal activity of the thyroid gland.

The chemical structure and composition of the obtained crystals were studied by Kendall and Osterberg (cited from Trendelenburg, /142/), who named this substance thyroxin, and gave the formula of its structure. But the correctness of the structural formula proposed by Kendall was questioned. The English researcher Harington later successfully solved this question and he has the honor of having established the correct formula of thyroxin in 1926, as well as its synthesis, which he realized together with Barger in 1927.

In this manner it was made clear that the veritable hormone of the thyroid gland is thyroxin and that thyroglobulin is a form of accumulation of iodine—the potential source of thyroxin.

The isolation of iodinated proteins with hormonal activity from the thyroid gland, and the discovery and separation of the active hormone from these proteinic preparations, in the form of an individual chemical compound, served as a powerful instigation for further research on the chemistry of thyroxin and thyroglobulin. This also gave great scope to the experimental and clinical research on the biochemical and physiological problems of the formation, metabolism and action of the thyroid hormones.

In order to obtain new results on the composition and characteristics of thyroglobulin, it was necessary to improve the technique of its separation and of the analysis of the products obtained from its hydrolysis. The researchers had a basic aim in elaborating the various methods of isolation of the iodinated proteins from the gland. on the one hand, to obtain homogeneous products which could be considered as pure substances, and on the other hand, to find out if the thyroid gland contains a mixture of iodoproteins corresponding to the various stages of halogenation and, if so, to separate them.

In order to obtain pure nondenatured proteinic preparations, it was proposed to use extraction, at a temperature of 0°, from the frozen microscopic sections of the organ, by means of an isotonic solution of sodium chloride and precipitation of the iodoprotein by ammonium sulfate at 35 to 45% saturation. The homogeneity of the preparations obtained in this manner could be proved, by the sedimentation rate during ultracentrifugation and by the method of electrophoretic separation /349, 350, 399/. The question whether there are several thyroglobulins in the thyroid gland remained unsolved.

A number of authors /264/, having obtained thyroglobulins in various stages of iodination from extracts of the gland, suspected the presence of heterogeneous proteins in the thyroid gland It is very probable that the degree of iodination of thyroglobulin may be subjected to considerable change depending on various factors.

Derrien /264/, Stanley /544/, Easty and others /282/, recently subjected these problems to new study. They made experiments using a new method of separating thyroglobulin, which was elaborated by Derrien /264/ This method, which [illegible]

of the thyroid gland by this method They showed a constant solubility in the presence of certain neutral salts and, under equal conditions of pH and temperature, they were homogeneous from the electrophoretic and immunological point of view. These

fractions were found to be very sensitive to changes of pH. An increase in acidity (pH $<$ 5.0) led to a considerable reduction of their solubility. The verification made by the authors of the present work of the preparations obtained by the early methods of Oswald, Heidelberger and Palmer (cited from Derrien, /264/) showed the presence of considerable quantities of noniodate admixtures in them, and in some cases also of denaturation products of thyroglobulin. The solubility of the pure, nondenatured preparations of thyroglobulin did not depend on their containing iodine and iodinated amino acids Besides this, this protein showed under certain conditions an identical composition in all its fractions, which were separated by consecutive precipitation in increasing concentrations of neutral salts. Thus, it follows that the iodine content of thyroglobulin is very variable and cannot be the criterion for the degree of purity of the preparation

Thyroglobulin is thus, very probably, a protein with a practically stable structure Noniodinated amino acids, whose degree of iodination varies enter into its composition, but under different physiological conditions. All three fractions of thyroglobulin, from extracts of the thyroid gland as well as from purified preparations, contain equal amounts of iodine and probably correspond to various degrees of association of thyroglobulin.

Studies made in our laboratory by V. M. Sorokin show that the ratio percent of the various fractions of thyroglobulin separated by the method of Derrien changes from one case to another

The question of possible differences in the properties of thyroglobulin under normal conditions and in pathology of the thyroid gland was subjected to a series of studies. The results which have been published do not give the basis for conclusion about any kind of difference in the amino acid composition of the preparations of the iodinated protein obtained from a normal thyroid gland and those obtained from an adenomatous or an exophtalmic goiter. Differences were observed only as to ratios between the quantity and the relationships of the iodinated amino acids.

The determination by electrophoresis and immunological reactions of the purity of thyroglobulin, secreted by the same patient from normal and carcinomatous tissue of the thyroid gland, showed that the protein fractions in both cases changed as identical compounds, but their mobility differed. Three or four antigenic components were discovered in every thyroglobulin.

Derrien and others also studied the thyroglobulin of four types of mammals (ox, horse, dog, and hog) in order to answer more specifically the following question: do they have any specific particularities, as was for example determined in the case of insulin, hemoglobin, etc? But analysis could not bring to light any differences between the thyroglobulins of the animals studied.

The iodine content of thyroglobulin determines its quantity in the colloid and in the whole thyroid gland, as 90-95% of the iodine in the gland are bound in the composition of the specific protein in the form of iodinated amino acids. As a result of alkaline or enzymatic hydrolysis of thyroglobulin, a series of iodinated derivatives of tyrosine and thyronine, characteristic only of the specific protein of the thyroid gland, are also separated together with the basic amino acids. According to the results of Bersin (cited from Jende, /357/), the amino acid composition of thyroglobulin is the following (grams of amino acids per 100 g protein):

Thyroxin	0.21	Tryptophan	2.1
Triiodothyronine	0.05	Cystine	3 6
Diiodotyrosine	0.5	Tyrosine	3.2
Monoiodotyrosine	0.6	Methionine	1 3
Monoiodohistidine	0.02	Alanine	7.4
Histidine	2 2	Glycine	3.7
Arginine	12.7	Valine	1.45
Lysine	3.4	Leucine	12 8
Phenylalanine	6 7	Serine	10.8

As has been previously noted, the quantity of iodinated amino acids in the molecule of thyroglobulin may also vary considerably in a normal thyroid gland, depending on a series of conditions. But more considerable fluctuations of their quantities are observed in various forms of pathology of the gland. These problems will be examined later in greater detail.

Thyroglobulin is not very soluble in water and in acids, but is very soluble in solutions of alkaline and neutral salts. It is precipitated from alkaline solutions by acids. The molecular weight of thyroglobulin is 675,000. It has a characteristic absorption spectrum of ultraviolet light with two absorption maxima: one at 2,800 A, depending on the presence of aromatic amino acids and of tryptophan in the molecule, and the second at 3,200-3 300 Å, which is determined by the presence of chromophoric groups of thyroxin and diiodotyrosine, and is consequently more specific for thyroglobulin.

Another protein, containing phosphorus, was also isolated from the thyroid gland by Oswald. This protein is a nucleoprotein, found in all cells. It has no specific property characteristic of the thyroid gland.

Notwithstanding intensive study of the synthesis of thyroid hormones, results on the chemical composition and the metabolism of the gland itself are rather scanty. In the composition of the gland, apart from thyroglobulin and nucleoproteins, there are also fats and lipoids, polysaccharides, inorganic salts, vitamins, and a whole series of enzymes. The water content of the gland reaches 75%.

Ribonucleic acid (RNA) and desoxyribonucleic acid (DNA) in the cytoplasm, nucleus, and nucleolus were studied in hyper- and hypothyroid animals. An increase [illegible] under the influence of propylthiouracil. The use of thyroxin, Lugol's solution, and hypophysectomy, lead to the reduction of DNA in the nucleus. On the basis of the basophilic staining of the colloid, it is assumed that the colloid contains a considerable amount of RNA This is confirmed by the fact that upon digestion of the colloid by ribonuclease, the basophilic staining reaction disappears progressively.

The presence of unusually great quantities of hydrolysable hexosamine was determined in the thyroid gland On the basis of histochemical reactions, Gresch (cited from "The Hormones", /358/) expressed the opinion that the polysaccharids, and to some extent hyaluronic acid, are found in the colloid in the form of glucoprotein The presence of glycogen in the thyroid was not determined

A considerable quantity of fats and lipoids is found in the tissue of the thyroid gland A series of works were recently published, examining the various aspects of the metabolism of phosphorus in the thyroid gland, and especially the metabolism of phospholipids. Morton and Schwarts /430/ reported on the selective absorption of P^{32} by phospholipids of the thyroid gland of cows, under the influence of the thyrotropic hormone, and Ingbar and Freinkel /311/, while studying the synthesis of the

thyroid hormone, determined on sections of the thyroid gland that the first stage of synthesis, which is the accumulation of I by the gland, depends on the supply of energy from oxidative phosphorylation. In his recent work, Freinkel /310/ studied the incorporation of P^{32}, glycerin, and labeled C^{14} into the composition of the phospholipids of fresh sections of the thyroid gland. After incubation the phospholipids were separated by chromatographic method. The presence of phosphoglycerides was proved in the lipid extract. The absorption of P^{32} by various fractions of the phospholipids varied, and also depended on the state of the thyroid gland. This *work showed that it is not possible to consider phospholipids as one fraction and* that it is possible to separate them in the gland into several fractions, each of which has its metabolic particularities.

Together with V.M. Sorokin /148/ we recently studied the distribution of P^{32} in the phosphorus fractions of the tissues and organs of rats under various functional states of the thyroid gland The method of determination of the phosphorus fractions in one portion of tissue elaborated by Sorokin and Ioffe /134/ was found to be extremely convenient for this research. Twenty-four hours after administering to the rats one μ of $KH_2P^{32}O_4$ per one gram of body weight the animals were killed and small pieces of the organ were rubbed into the pores of a circle of filter paper. The tissue was then extracted from the circle of paper by a mixture of ether, alcohol and acetone (lipoid phosphorus), cold trichloroacetic acid (inorganic phosphate) hot trichloroacetic acid (nucleic phosphorus), and then the residue (proteinic phosphorus) was determined After each extraction a reading of the activity on the circle was made The results on the distribution of P^{32} in the phosphorus fractions of the tissue of the thyroid gland of healthy rats, obtained by V M Sorokin and K G Ioffe, showed approximately the same activity for the thyroid gland, kidneys, epiphysis, and spleen. The adrenal glands, and particularly the liver, absorbed considerably more, and the pituitary and brain had a markedly low absorption of P^{32} In a normal thyroid gland, 24 hours after the administration of $KH_2P^{32}O_4$, almost half of the activity was in the inorganic phosphate, 20-24% of the total activity in the lipoid phosphorus, 18-20% in the nucleic phosphorus, and only 6-8% in the proteinic phosphorus. In rats treated with thyroidine for one month we noted a certain rise in the absorption of phosphorus and a marked change of its distribution among the fractions. the percentage of inorganic phosphate dropped to 36-41, nucleic phosphorus also decreased, the activity of the lipoid fraction rose considerably, and that of the protein rose even more (14-20%). This evidently points to an increase of the synthesizing processes in the thyroid gland under the action of the thyroid hormone

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The thyroid gland was also studied from the histochemical point of view. The presence of a whole series of enzymes in the gland was shown by the use of a histochemical technique. Thus, Dempsey /261/ discovered peroxidase granules. The presence of phosphatase, protease, and oxidase were also determined in the gland /263/. The quantitative study of these enzymes was made at various physiological states of the gland. Research made in the Laboratory of Pathohistology of the Institute of Regional Medicine of the AS Uzbek SSR confirmed the presence of acid and alkaline phosphatases and peroxidase in the gland.

Among inorganic substances the gland was shown to contain, apart from iodine, Cl, Br, F, Mn, Mg, S, Zn, Ti, Sn, Pb, Al, U, Ag, Fe, Hg, Si, Rb, Li, As, Cr, Co, Ni. In the thyroid gland the accumulation of elements from group VII of Mendeleev's table occurs to various extents, but only iodine enters into the organic bond, and this permits it to become concentrated in comparatively large quantities Other elements of group VII do not remain in the thyroid gland and therefore they leave the organism speedily when administered in considerable doses. Thus, for example, Rhenium, administered in the form of labeled $HRe^{186}O_4$, was concentrated in the gland from 25 to 100 times more than in the blood, but as a result of its speed of excretion in the urine the activity of Rhenium in the organism is lost after two days Mn is also absorbed and speedily lost. It was determined, however, that all these elements displace iodine to a certain extent from the thyroid gland, and they all provoke goiter when present in sufficient quantity. Information also exists on the augmentation of the goiterogenic action of thiourea by bromides, chlorides, and fluorides.

A large number of studies exist on fluorine and bromine, especially in relation to efforts to determine the possible role of fluorine in the etiology of goiter and the antagonistic relationships between iodine on one side, bromine and fluorine on the other In the human thyroid gland there are 0.9-1.4 mg% of bromine and in the gland of dogs 0 84-1.46 mg % (F.Ya. Berenshtein /20/).

E S Turetskaya /150/ studied the ratio of iodine and bromine in the thyroid gland of persons inhabiting the western regions of the USSR who died in accidents According to her results, the ratio for people living in the above regions, where an iodine deficiency in the surrounding environment is noted, is less than 8 6 percent and the absolute value is 6 6, while in persons who are not local inhabitants both values were 7.2.

I.N Verkhovskaya /28, 29/ brings results on the antagonistic relationship between iodine and bromine in the thyroid gland Together with Tsofina /30/ she observed augmentation of bromine in the thyroid gland during thyrotoxicosis. Normally at 0 77 mg %, thyrotoxic patients took up about 1.70 mg % of bromine After administration of preparations of iodine the bromine content is reduced The administration of preparations from the thyroid gland also provokes a reduction of the bromine in the blood

The content of astatine (ecaiodine) in the thyroid gland of guinea pigs, rats, monkeys, and humans was from one tenth to one fourth of the content of iodine This element may assume therapeutic importance, as it liberates α -particles during its disintegration.

It was also determined that the accumulation of antimony in the thyroid gland is greater than that in any other organ

Sulfur in the form of S^{35} appears in the colloid after 48 hours in quantities sufficient for autoradiography Our research /147/ also showed an intensive inclusion of S^{35} methionine in the proteins of the thyroid gland of normal and hyperthyroid rats. Sulfur, administered in the form of thiourea, appears and becomes localized in the thyroid gland, where it is speedily oxidized into sulfates.

As has already been noted, our results on the chemical anatomy and metabolism of the thyroid gland itself ...

biochemical and cytochemical methods

In view of the fact that the absorption of iodine, its metabolism in the gland, and the secretion of iodine-containing hormones are the essence of the biochemical processes of hormone formation in the thyroid gland, each of these questions shall later be examined separately.

2 The Fixation of the Iodides of the Blood by the Thyroid Gland

The first and indispensable condition for the beginning of intrathyroidal metabolism of iodine is the trapping of iodides from the blood stream by the thyroid gland. *The capacity of concentrating iodides from the blood is actually the most important particularity of the thyroid gland*

The trapping of iodine from the blood by the thyroid gland occurs very quickly. About 2.5% of the inorganic iodine of the plasma accumulates hourly in a normal gland This corresponds to the decontamination of the plasma from iodine by the thyroid gland which is equal to about 10 ml per minute, in hyperthyroidism the accumulation rises to 20 % per hour, constituting 130 ml of plasma per minute. All the other tissues, except the kidneys and thyroid gland, use only 2% of the iodides of the plasma, and their general activity is only 12% of the iodine pool.

The iodine ions are found in blood plasma in very low concentrations, of about 0.1-0 5 μg per 100 ml, and a very active concentration mechanism ensuring constant accumulation of iodides in the cells is necessary, so that such a minute quantity of iodine could be included into the metabolic cycle. Such a mechanism exists in the thyroid gland. The fixation of the iodides of the blood by the thyroid gland consists of two consecutive stages: the actual accumulation of iodine in the real sense of the word, and its oxidation into elementary iodine - I_2

Iodine can react with thyroglobulin in order to be included into the organic combination only in its elementary form But also in the absence of organic binding of iodine the thyroid gland can accumulate it at least to the same extent as the salivary glands or the gastric juice, i e , up to a level of 40-50 times higher than the quantity of iodine in the plasma It is impossible to draw a line between this part of the fixation of iodine and the following stage, when the oxidation of iodide into elementary iodine takes place with its immediate inclusion into the protein molecule. Under normal conditions the organic binding of iodine in the gland takes place so fast that no considerable concentration gradient - $\frac{\text{iodine of the thyroid gland}}{\text{iodine of the plasma}}$ is reached and the quantity of free iodine in the gland does not constitute important quantities in the general iodine pool of the organism

The process of concentration of iodine-I' in the thyroid could be studied with precision only by the use of labeled iodides and antithyroid substances, capable of breaking the chain of the transformation of iodine into its different links. It must be remembered that results, which would be valuable from the physiological point of view, can be obtained only by using such quantities of iodine which do not perceptibly rise above the level of iodemia.

Iodides administered to a rat in doses from 100 μg to one mg penetrate into the thyroid gland to a very small extent and do not remain in it, for at that stage they do not yet participate in the formation of iodinated amino acids. Iodides are excreted by the kidneys, the digestive tract, bile, and saliva and the metabolism of the I ions becomes normal when the level of iodemia returns to its initial value. It is only possible to follow the fate of iodides after administering 1-2 μg of labeled iodine to a rat. This concentration is already perceptible a few minutes after injection, as may be shown by radioautographic study of microscopic sections of the gland

One hour after administering physiological quantities of radioiodine the concentration of I^{131} in the organ is 500 times higher than that of the blood and all the administered iodine may be fixed by the gland within 8-12 hours. I^{131} can be already found in the colloid less than 30 seconds after its administration. Our research /149/, with the administration of considerable quantities of I^{131} (one μC per gram of live weight) to rabbits, enabled us to discover the accumulation of radioactive iodine in the thyroid gland already 10-15 seconds after an intravenous injection Analogous results were also obtained by other authors /98, 614/. The penetration of iodine into the cells of the thyroid gland may be shown by the following diagram (Figure 1).

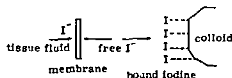


Figure 1. Schematic representation of the state of iodine in the thyroid gland

Free iodine is in equilibrium with the iodine of the blood stream. On the other hand, free iodine is also in equilibrium with bound iodine, which forms an unstable combination with the colloidal system and may pass through the membrane.

The autonomous nature of this first phase of the intrathyroidal metabolism of iodine was clearly demonstrated in research by means of blocking the oxidation reaction of the iodides into I_2 in the gland, which is effected by sulfonamides and preparations of thiourea. Such research was initially conducted by the workers of Chaikoff's group /308, 518/ and by others, who observed that although the capacity to bind iodine in an organic form is weakened in sections of the thyroid gland in the presence of sulfonamides and thiouracil, they maintain their capacity to concentrate iodine. The same thing happens when propylthiouracil is administered to the animals.

Thus, a thyroid gland blocked by thiouracil may capture iodine and contain it in concentrations several hundreds of times higher than the concentration of iodine in the plasma Under these conditions, iodine is accumulated in the gland in the form of thyroglobulin salts, instead of being included into the iodinated amino acids. As can be seen from the above diagram, this is a "weakly combined iodine". When blockade is total, the iodine entering the thyroid gland is in an inverse ratio to the iodides of the plasma and, in contrast to iodine accumulated and bound in an organic form in the unblocked gland, may be easily forced out by thiocyanate, perchlorate, and some other anions /545, 591, 597/.

The capacity of the thyroid gland to concentrate I^{131} may be expressed either by the relation of the iodine concentration of the thyroid gland to the iodine of the plasma, or by the thyroid iodine volume in liters, equivalent to the iodine of the plasma The iodine volume of the thyroid gland depends on its size, as well as on the iodine concentration ratios. In thyrotoxic persons the concentration gradient may be 500 : 1; the thyroid iodine volume may contain a quantity of iodine equivalent to that of 30–35 liters of plasma /214, 215/ A blocked normal thyroid gland has a thyroid-iodine volume of very rarely more than 400–500 ml of

plasma, but a rise of the concentration gradient was observed within 8-9 hours, under the influence of thyrotropic hormone.

Physiologically iodine is integrated into organic compounds immediately after entering the gland. At the same time, only a minute quantity of iodine, not more than 2% of its total quantity in the thyroid gland, is found in the form of iodides, and may return as such to the plasma. This is in accord with the known results, that already after 1-2 minutes of accumulation by the unblocked thyroid gland, I^{131} is not forced out by thiocyanate. A part of the iodides in the gland is formed by dehalogenation of the iodotyrosines liberated from thyroglobulin during the process of proteolysis.

Insufficient organic binding of iodine in the thyroid gland may also take place without the use of specific antithyroid substances, for example in some cases of thyroid cretinism.

The mechanism of the capture of iodine from the plasma by the thyroid gland was studied by many authors, but it is still insufficiently clear today. In order to explain the process of the accumulation of iodine in the thyroid gland against the concentration gradient, a number of authors directed their attention to the energetic aspect of the functioning of the gland, /311/. The indispensability of aerobic conditions for the concentration of iodine by the thyroid gland was shown in studies with sections of the thyroid gland of animals in a Warburg apparatus. The accumulation of iodine by the sections was lowered at temperatures and values of pH which were too high. Optimum conditions for the capture of iodine by the glands were pH = 7.5-8.0, and a temperature of 35-40°. Studies of the capture of iodine by sections of the thyroid gland with simultaneous measuring of the absorption of oxygen showed that the minimal transport of iodine demands simultaneous expenditure of energy supplied by the aerobic cellular metabolism. There is a definite direct relation between these two processes. The results of Freinkel and Ingbar /311/ show that an active, metabolically-bound oxidation process is an indispensable condition for the transport of inorganic iodine into the thyroid gland against the concentration gradient.

The transport of iodine into the thyroid gland ceases when inhibitors of aerobic respiration (cyanide, azide, sulfide, arsenite, phlorizin, fluoroacetate, etc) are added to the incubation medium; this also occurs by the addition of many compounds reacting with the sulfhydryl groups (Hg, Zn, Cu, iodoacetate, bromoacetate, quinone, p-chloromercuribenzene, 2,3-dimercaptoimidazole). These substances do not necessarily also suppress respiration of the tissues.

The absorption of iodine is also lowered by the action of sulfonamides, inhibitors of oxidative phosphorylation (2,4-dinitrophenol, 2,4,6-trinitrophenol etc) considerable quantities of iodide, thiocyanate, perchlorate, etc.

While studying the absorption of iodine by the thyroid gland in patients suffering from myxedema, N.A. Gabelova /37/ discovered that the absorption of iodine by *these patients corresponds to the capture of iodine during* blockade of hormone formation in the gland under the action of thiouracil. In this condition the quantity of radioiodine in the thyroid gland during the initial absorption period rises in proportion to the square root of the time that has elapsed since the administration of radioiodine. Thus, Gabelova postulates a diffusion-like absorption of radioiodine by the thyroid gland, emphasizing that this process is not a purely physical one, but is under the regulating influence of the nervous system. She explains the high concentration gradient in the thyroid gland by the high "solubility" of iodine in the gland, and this is why, according to her opinion, the absorption of iodine by the thyroid gland against the gradient of concentration goes on quite easily, without loss of energy in order to overcome osmotic forces. Most of the energy used in the process of the vital activity of the thyroid tissue is expended in order to maintain

the functional and consequently also the structural organization of the tissue. As is supposed by Gabelova, the excretion of iodine from the organism also takes place by diffusion, corresponding to the formula that she elaborated, which is analogous to that of absorption by the thyroid gland.

However, according to the opinion of most researchers, the clearance of iodine by the thyroid gland and the kidneys follows two analogous exponential curves. This opinion is firmly based on a great number of experimental and clinical observations.

N.A. Gabelova's opinions are based on the mathematical treatment of only a few cases, and the arguments put forth are insufficient. Besides, the assertion of a better "solubility" of iodine in the gland than in blood, which ensures the direction of diffusion against the gradient of concentration, is absolutely unfounded. As was shown previously, the process of iodine capture demands simultaneous oxidative metabolism, and this is why Gabelova's opinion on the "drifting" of iodine from the blood into the gland, without loss of energy, is also speculative.

It is possible that the initial capture mechanism of iodine by the thyroid gland does not differ in principle from the same mechanism in other tissues. But, if we consider the later fate of thyroid iodine and the extremely high gradients of concentration, which the thyroid gland is capable of holding against the plasma, capture of iodine by the thyroid gland stands in a position by itself.

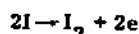
It was previously thought that the fixation of iodine by the thyroid gland is only possible in the presence of an intact cellular structure. Although sections of the thyroid gland actively absorb iodine from the surrounding medium, raising the concentration gradient $\frac{\text{gland}}{\text{medium}}$ to high values, it was not possible to show absorption of iodine by homogenates of the tissue.

The capacity of gland tissue homogenates to concentrate iodine from the surrounding medium has been shown in recent years by a series of studies. Myngarden and Stanbury /436/ studied the absorption of I^{131} from the surrounding medium by gland homogenates which were kept in small dialyzing bags. It was discovered that after 24 hrs of incubation the activity ratio $\frac{\text{homogenate}}{\text{medium}}$ reaches 6, but in the majority of cases it was equal to 3. The greater part of I^{131} captured by the gland was found to be in the form of I_2, which is extractable by carbon disulfide only to a small extent; it was then redialyzed. Only 20-30% of the iodide was included in the protein molecule and gave after hydrolysis monoiodotyrosine and small quantities of diiodotyrosine

3. The Oxidation of Iodide in the Thyroid Gland into Elementary Iodine

During the concentration process in the thyroid gland the iodides do not undergo any transformation. This is shown by the speedy falling off of radioactivity in the thyroid gland of animals to which preparations having the capacity of forcing out unbound iodine from the gland, as for example thiocyanate (rhodanide), or perchlorate, were administered following radioiodine.

The indispensable condition for the organic binding of iodine is the oxidation of iodide with the formation of elementary iodine, together with its accumulation in the thyroid gland:



$$2I \rightarrow I_2 + 2e$$

plasma, but a rise of the concentration gradient was observed within 8-9 hours, under the influence of thyrotropic hormone.

Physiologically iodine is integrated into organic compounds immediately after entering the gland. At the same time, only a minute quantity of iodine, not more than 2% of its total quantity in the thyroid gland, is found in the form of iodides, and may return as such to the plasma. This is in accord with the known results, that already after 1-2 minutes of accumulation by the unblocked thyroid gland, I^{131} is not forced out by thiocyanate. A part of the iodides in the gland is formed by dehalogenation of the iodotyrosines liberated from thyroglobulin during the process of proteolysis.

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Later works of Wollman and Wodinsky /514/ showed that, after injection of radioactive iodine to normal mice, radioautograms appear after 11-16 sec. In rats they appeared after 30 sec and only in the colloid, not in the cells. The problem nevertheless remains unsolved: does the iodinated protein form in the cells and is then, very shortly after, secreted in the colloid, or does it form in the colloid, at the surface of the cells? In any event the fact remains that iodine bound to the protein appears in the colloid as early as 10 sec after the injection of radioactive iodine into the blood stream. If we take into account that, before inclusion into the tyrosine molecule, the inorganic iodide has a very long way to go in the blood stream, that it passes through a series of membranes and undergoes at least one chemical transformation, namely—the oxidation into atomic iodine, the astounding speed of the whole process of hormone formation becomes evident. The discovery of absorbed iodine inside the follicular lumen /456/, and the evident indispensability of intact cells for the effective iodination of thyroglobulin concur with the hypothesis that the cells secrete, independently, thyroglobulin and iodine in the follicles. But cellular activity in the apical region is indispensable for the oxidation of iodine in the process of iodination of the combined thyroglobulin. It should also be taken into account that, if the oxidation of iodide takes place inside the cells, the proteins of the cells themselves may successfully compete with thyroglobulin for the possession of elementary iodine. Anyhow, the basic mass of iodine is found in the form of thyroglobulin and a relatively small quantity of the iodinated amino acids are formed by intrafollicular proteolysis of thyroglobulin.

The anatomical localization of the process of hormone formation in the thyroid gland was studied by M.F. Merkulov /97, 98/ in recent years by the autoradiographic method. His study on rats, on the localization of radioiodine in sections of the thyroid gland 10 sec, 20 min, and other longer time intervals after the administration of radioiodine, make it possible for the author to affirm that the iodination of thyroglobulin takes place in the colloid of the thyroid gland in view of the fact that, 10 sec after the administration of radioiodine, the iodinated protein is found only in the colloid. Further on, taking into account the distribution and intensity of the immediate initial absorption of radioactive iodine, the author supposes that, at least in regard to the capacity of concentrating iodine, only 5% of the total quantity of follicles function simultaneously. The distribution of labeled thyroglobulin, 20 min after intravenous injection of I^{131}, shows a different degree of secretion of radioiodine in the colloid by the follicular cells. The labeled protein is found in the follicular cells after longer lapses of time and, as is pointed out by the author, this probably reflects the secretion process of the iodinated compounds into the blood stream.

Analogous results were obtained in our laboratory by Islanbekov /149/, from autoradiographic study of the thyroid glands of rats and rabbits. We administered intravenously to rabbits large doses (one μC per gram of body weight) of radioactive iodine and studied the localization of activity, after various time intervals, by the autoradiographic method on microscopic sections of the gland; at the same time, we performed radiochromatographic determinations of the iodine-containing components of the blood and gland. [illegible]

shown by the fact that 10 sec after the administration of radioiodine the activity in the colloid is discovered not in the central parts of the follicle, but in a rather narrow band very close to the apical region of the follicular cells.

Another important question which is worth examining is that of the role of the cellular structures, or of the indispensability of the intact structure of the epithelial

It is still not clear whether this process takes place with the participation of a special enzyme, or whether oxidation can take place in a non-enzymatic manner. This reaction may be experimentally reproduced in vitro by means of various oxidizers, under the influence of such enzymes as peroxidase and cytochrome oxidase, whose presence in the thyroid gland is well known. But, no one has yet succeeded in isolating free elementary iodine from the thyroid gland, though in recent studies by Fawcett and Kirkwood /288/, who studied the formation of organically bound iodine in homogenates of the thyroid gland, upon adding copper and tyrosine to the incubating medium, the appearance of spots corresponding to iodine atoms was shown on chromatograms As these authors note, copper in this reaction probably enhances the oxidation of iodide to iodine. Evidently the oxidation of iodide takes place very speedily, and the free iodine which is formed is immediately incorporated into the thyroglobulin molecule or into the free amino acids, taking on an organically bound form.

As may be seen from the above-mentioned work, Fawcett and Kirkwood assumed the oxidation of iodide as also taking place in a non-enzymatic manner. The presence of copper ions and tyrosine, which later is the acceptor of elementary iodine, suffices for this. Copper may be replaced by iron and by hydrogen peroxide.

But the suppression of the process of organic binding of iodine in the thyroid gland by antithyroid substances, and the accumulation of iodides in the thyroid gland as a result, prompts us to assume the participation of oxidative enzymes in this process, as there are proofs /261/ that thiouracil and agents that are analogous to it suppress the activity of peroxidase and of cytochrome oxidase. It was proved, for example, that there is a strong inhibition of activity of peroxidase by thiouracil and of cytochrome oxidase by cyadine and thiourea. In addition, the antithyroid substances are also restoring agents, and they lower the oxidation-reduction potential of the epithelial cells.

All that has been said on this problem convinces us of the fact that the transformation of iodide into I_2 deserves further research, as its enzymatic mechanism has not yet been definitely cleared up, although the transformation rate $I' \rightarrow I_2 \rightarrow$ organically bound iodine rather points to an enzymatic pathway than to any other.

4. The Incorporation of Iodine into the Organic Compounds of the Thyroid Gland

The elementary iodine which is formed during the oxidation process is immediately included into the protein or the free amino acid molecules.

One of the unsolved problems of the hormone formation physiology is the problem of the anatomic localization of this process. Where does the organic binding of iodine take place? A series of carefully performed studies with radioautographs did not give a definite answer to this question. In order to determine the role of the epithelial cells and of the colloid in the formation process of iodinated thyroglobulin, studies were made on the distribution of radioactivity in the various structural elements of the gland at different time intervals after the administration of radioactive iodine. Leblond and Gross /394/ observed that after administering I^{131} to animals with a blocked thyroid gland the earliest localization of radioactivity bound to protein appears in the apical part of the epithelial cells, which is adjacent to the follicular colloid. The distribution in the follicles is ring shaped. The autogram of the ring later moves to the center of the follicle. In animals living on a poor iodine diet and, consequently, having a stimulated thyroid gland, the earliest radioactivity was found in the colloid.

The role of tyrosiniodinase in the salivary glands may be that of deiodination of mono- and diiodotyrosine.

The most recent works touching upon the deiodination of diiodotyrosine and the enzymatic system of synthesis of monoiodotyrosine /542, 527/, showed the presence of two enzymatic systems catalyzing the synthesis of monoiodotyrosine in the cells of the thyroid glands, the salivary glands, and several other tissues. One system probably represents the enzyme described by Fawcett and Kirkwood; it is soluble, and forms free monoiodotyrosine after the addition of tyrosine and copper ions. The second system first discovered in the thyroid gland /567/, and later also in the tissue of salivary and mammary glands of rats /569/, was found to be related to the mitochondria of the cytoplasm. The mitochondrial system does not need any additions, and forms monoiodotyrosine bound to the protein. A close tie between these two systems was later found to exist.

The soluble enzymatic system which synthesizes monoiodotyrosine needs a supply of molecular oxygen for its function. It also needs the presence of hydrogen peroxide. Copper, in all probability, takes part in the process of peroxide oxidation of iodine or in the substitution reaction in the molecule of tyrosine, after the formation of H_2O_2.

The research by Weiss /604/ showed that anaerobic conditions, which almost completely stopped the conversion of I^{131} by sections, have no noticeable effect on the homogenates. He also determined that the enzymes participating in the formation of diiodotyrosine and thyroxin are localized in the nuclei and mitochondria, and that in the latter they are more active.

On the other hand, as a result of the research made by Taurog /567, 569/ with noncellular preparations of thyroid gland tissue, it follows that, for the formation of organic iodine by homogenates or by small fractions of the thyroid gland, the addition of tyrosine or of copper is dispensable, but during this process there is a formation of monoiodotyrosine bound to the protein, which is secreted only after hydrolysis of the protein by the thyroid gland.

The biosynthesis of monoiodotyrosine by the diluted homogenate of a hyperplastic thyroid gland was shown in the above-mentioned work of Myngarden and Stanbury /436/. But, upon incubation of the homogenates in small dialyzing bags, the main part of the included I^{131} was not in the form of iodinated amino acids, but was found in the form of a compound which was slightly extractable by carbon disulfide, and was then discovered in the form of elementary iodine. The utilization of iodine did not depend on addition of tyrosine, but copper had a strengthening effect. Thiocyanate and propylthiouracil totally suppressed the incorporation of iodine into the homogenate. The homogenate, freed of the cells and nuclei by centrifugation, had the same activity as the noncentrifuged one. Heated as well as unheated homogenates could utilize elementary iodine, but after boiling the homogenate copper had no promoting effect on it as to the capture of iodine. Even in the presence of copper heated homogenates cannot utilize iodide and, consequently, this means that the inclusion of iodide takes place after its oxidation into a neutral iodine atom. These results convince us again of the enzymatic character of the oxidation of the iodine ion—a process which is promoted by copper and evidently depends on the presence of peroxidase. The iodine included in the homogenate is mostly found in two forms: 50-70% in that of I_2, slightly extracted by CS_2, 20-30% in the form of monoiodotyrosine, and a very small quantity in the form of diiodotyrosine.

It follows from the above experiments that neither the absorption of iodine by the thyroid gland nor the formation of organically bound iodine demand the presence of an intact cellular structure of the gland, and that they are effected by different noncellular preparations of the gland The presence of enzyme systems, localized

cells in order to ensure the synthesis of the organically bound form of iodine. It is known that sections of the thyroid gland of sheep, man, dogs, or rats, form labeled organic compounds from I^{131}. It was thought earlier that intact cells of the thyroid gland are indispensable for this synthesis. But, organic binding of iodine by noncellular preparations of the thyroid gland was shown by the works of Fawcett and Kirkwood /288/, and Weiss /604/. Fawcett and Kirkwood showed by the radiochromatographic method that the organic compounds are formed from added inorganic iodide and tyrosine only in the presence of copper salts. As has been noted, the opinion of these authors is that, if the oxidation of iodide into elementary iodine does not need a special enzyme, then the reaction of the iodination of tyrosine is on the contrary an enzymatic process and is effected by a special enzyme which they named tyrosiniodinase.

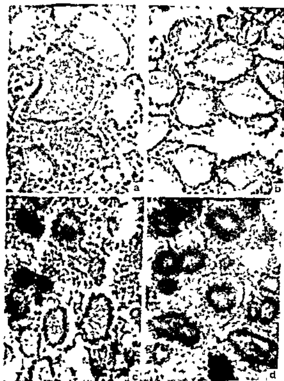


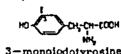
Figure 2. Autoradiograms of the thyroid gland of rabbits, at various time intervals after administration of I^{131}

a—30 sec, b—20 min, c—2 hours, d—24 hours, 280-fold magnification
[only appr 200-fold in this reproduction]

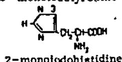
Tyrosiniodinase was studied in detail by the same authors /289/. This enzyme was also discovered in salivary glands, and its highest activity was found in the submaxillary gland, next comes the parotid gland, and the thyroid gland posseses about half the activity of the submaxillary gland. The action of the enzyme is reversible and the direction of the reaction depends on the oxidation-reduction state of the cell.

The presence of three iodine-containing substances in the thyroid gland: diiodotyrosine, thyroxin, and thyroglobulin was thus known before 1948. Events took on a further speedy turn with the use of radiochromatographic methods for the study of the composition of the iodine-containing components of the thyroid gland hydrolysates.

In 1948 K. Fink and R. Fink determined, in thyroid gland hydrolysates, the presence of another iodinated derivative of the amino acid tyrosine — 3-monoiodotyrosine /297/, and in 1952 Roche, Michel and Lissitzky discovered also iodinated histidine in the hydrolysates /484/:



3-monoiodotyrosine



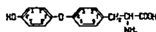
2-monoiodohistidine

The year 1952 was a historical landmark in the study of the biochemistry of the thyroid gland hormones, for another reason as well. In this year, the discovery was made of a very important iodinated compound of the thyroid gland, 3, 5, 3'-triiodothyronine, almost simultaneously by two groups of researchers: Gross and Pitt-Rivers /332/ in England and Roche, Michel, and Lissitzky /484/ in France.

The next important events were the identification of 3, 3', 5'-triiodothyronine in thyroglobulin, effected in 1954 by Roche, Michel, and Wulf /497/ and finally, the discovery of 3, 3'-diiodothyronine by Roche, Michel, Wulf, and Nunez /499/.

The presence of 3, 3'-diiodothyronine and 3, 3', 5'-triiodothyronine in the composition of thyroglobulin was doubted for a certain time, as a number of authors did not succeed in reproducing the results obtained by Roche, Michel, and their group. The opinion prevailed that these compounds are products of the dissociation of iodothyronines as a result of irradiation by large doses of radioactive iodine used in the experiments. But a long series of works made by the group of Roche and Michel /490, 492, 500/ followed. Later they convincingly proved the presence of the above two new iodothyronines in the composition of thyroglobulin

The presence of the following iodinated derivatives of tyrosine in the thyroid gland is accepted today: 3-monoiodotyrosine, 3,5-diiodotyrosine, and very small quantities of 2- or 4-monoiodohistidine having no hormonal activity. Four iodinated components, derivatives of one and the same structure, are related to the hormones of the thyroid gland: derivatives of l-thyronine or β - 4 (4-hydroxyphenoxyphenyl) l-aminopropionic acid.



thyronine

The iodinated derivatives of thyronine correspond to the formulas of 3, 3'-diiodothyronine (Roche, Michel, Wulf, Nunez, 1955) and 3, 5, 3'-triiodothyronine (Gross, Pitt-Rivers; Roche, Lissitzky, Michel, 1952), 3, 3', 5'-triiodothyronine (Roche, Michel, and Wulf, 1954) and of thyroxin or 3, 5, 3', 5' tetraiodothyronine (Kendall, 1915, Harington, 1926).

These derivatives of thyronine are the hormonal products of the thyroid gland secreted into the blood stream.

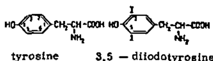
in the mitochondria and microsomes is absolutely necessary to ensure these functions of the thyroid gland.

5. Iodinated Amino Acids in the Thyroid Gland

The oxidation of iodides into elementary iodine and its inclusion into the thyroglobulin molecule is the first stage in the biosynthesis of the hormonally active compounds in the thyroid gland. Further stages of hormone formation include the synthesis of iodotyrosines, the condensation of molecules of mono- and diiodotyrosines with the formation of thyroxin, the enzymatic liberation of iodinated amino acids, and the secretion of the completed hormones into the blood.

After having determined the structure of thyroxin, Harington assumed that thyroxin is formed by way of condensation of two molecules of diiodotyrosine - the only iodinated amino acid then known. The composition of the iodinated compounds formed in the thyroid gland and emitted into the blood stream is at present sufficiently studied due to the use of radioactive iodine and of chromatographic separation of the iodinated compounds of the thyroid gland.

Diiodotyrosine is the first iodinated compound the presence of which in the gland was determined almost simultaneously with the studies on the chemical composition of the thyroid gland, made by Baumann at the end of the last century This iodinated derivative was discovered in 1896 by Drecksel (cit. from Roche, Michel, and Jouan, /484/).



tyrosine   3,5 — diiodotyrosine

The presence of sufficient quantities of diiodotyrosine in the thyroid gland was confirmed in 1931 by Harington and Randall /346/by its secretion from the gland.

But this component had no hormonal activity.

A series of active preparations was obtained as a result of hydrolysis of iodothyroglobulin, but they were found to be insufficiently pure products of the dissociation of the iodine-containing protein. Numerous persistent studies led at last to the obtaining of a pure preparation, possessing the biological action of the thyroid gland. As is known, this was accomplished by Kendall, who separated crystalline thyroxin from the hydrolysate of thyroglobulin, in 1915. The next stages in the study of the hormones of the thyroid gland were: the determination of the formula of thyroxin by Harington in 1926 and the synthesis of this compound by Harington and Barger in 1927 (cit. from Trendelenburg, /142/). After this, methods were elaborated for biological evaluation of the hormonal activity of thyroid preparations, by the rise of basal metabolism of rodents or by the speeding up of amphibian tadpole metamorphosis. During the forties of our century, iodinated proteins possessing thyroid activity were successfully obtained from casein and other proteins. Although the obtaining of these proteins was announced as early as the beginning of the thirties, this question was definitively answered in 1939, [illegible] (cit. from Kameron, /73/) succeeded in

Results obtained by us /149/ also showed the appearance of free thyroxin, first in the composition of the gland, only later in the blood stream.

The presence of free iodinated amino acids is thus an indispensable condition for the entry of the hormone into the blood stream. In any case, free hormones do not accumulate in the gland itself

The relationship of the iodinated components in the thyroglobulin molecule was studied by many researchers, using radioactive iodine, after administration in vivo, as well as after in vitro incubation of sections and homogenates of the thyroid gland /143, 544, 436, 568/.

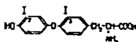
It follows from these works that the relationship of the iodinated components in the hydrolysate of the thyroid gland, 24 hrs after the administration of radioactive iodine, remains more or less constant in all cases. About 60% of the radioactivity is accounted for by the mono- and diiodotyrosines. The thyroxin and triiodothyronine iodine amounts to 25-30%. In chromatography of gland hydrolysates of animals having received radioiodine a certain part of the radioactivity remains in the place of application and another part spreads on the chromatogram The relationship between the iodinated amino acids changed in tests made at various intervals after the administration of radioiodine and it also depended on the method of hydrolysis Some discrepancies in the results of different authors may probably be explained by the experimental conditions.

In our laboratory we studied by the chromatographic method the composition of iodinated compounds of thyroid gland hydrolysates 15,30 sec, 20 min, 2,24,and 72 hrs after the administration of large doses of radioiodine to rabbits. We compared the results obtained on the distribution of activity in the iodinated components on chromatograms with the results of the autoradiograms of the gland /149/. The radiochromatograms of the butanol extracts of the gland hydrolysates show that after 15 sec it is already possible to determine a considerable activity corresponding to monoiodotyrosine and an almost imperceptible activity in the spot of diiodotyrosine. The basic activity is found in the form of iodide. After 30 sec the same activity is centered in diiodotyrosine as in monoiodotyrosine. Noticeable activity in the thyroxin fraction appears considerably later, it increases constantly and reaches 25-30% of the total activity, 24 hrs after the administration of radioiodine. The radiochromatograms of the butanol extracts of the hydrolysates of thyroid glands of rabbits after various intervals of time are shown in Figure 3.

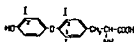
It was shown in a great number of studies that about 3/4 of the thyroid hormones in the gland are found in the state of thyroxin L-thyroxin is isolated in a pure state from the enzymatic or barium hydrolysate of the gland. Its presence is proved on radiochromatograms of the butanol extracts of the thyroid gland after administration of labeled iodine. Notwithstanding the discovery of other iodinated thyronines, possessing physiological activity, thyroxin remains the basic hormone of the thyroid gland and contains most of the hormonal iodine of the gland as well as of the plasma.

As was already noted, the presence of 1-3, 5, 3'-triiodothyronine in thyroglobulin was determined almost simultaneously by Gross and Pitt-Rivers in London and by the group of Roche in Paris. But Gross and others /331/ showed even before [illegible]

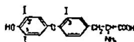
[illegible] thyroid gland of rats after administration of radioiodine. Its quantity is subjected to considerable fluctuations and does not rise above 1/5 of the quantity of thyroxin.



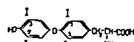
3, 3'-diiodothyronine



3, 5, 3'-triiodothyronine



3, 3', 5'-triiodothyronine



3, 5, 3', 5'-*tetraiodothyronine* (thyroxin)

All the natural iodinated amino acids, secreted from the thyroid gland, are derivatives of the l-isomers of tyrosine and thyronine, and they also possess the l-configuration and optical activity. The hormonal activity of the d-isomers of thyroxin and triiodothyronine is incomparably lower, as will be shown, than that of their natural antipodes.

The following abbreviations which we shall also use are accepted in scientific literature, as proposed by Harington, Pitt-Rivers and others /347/, for the iodinated amino acids from the thyroid gland *and their derivatives thyronine-T, monoiodo*-thyronine-T_1, diiodothyronine-T_2, triiodothyronine-T_3, thyroxin-T_4, monoiodo-tyrosine-MIT, diiodotyrosine-DIT. The position of iodine in the first and second benzene rings is shown by numbers: for example, for the triiodothyronines, 3, 5, 3'-T_3 and 3, 3', 5'-T_3.

The main mass of the iodinated amino acids in the thyroid gland is found in a bound state in the composition of thyroglobulin, and is separated from it during hydrolysis. The quantity of free iodinated compounds is relatively low.

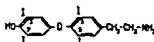
In the thyroid gland of man and of most vertebrates hormonal iodine is *about one third of the total quantity of iodine. About 2% of the iodine is found in* the form of low molecular compounds (amino acids, peptides) and the remainder is included in the molecule of thyroglobulin. The biological importance of this specific glucoprotein is that it contains all four iodinated parts of the hormone as structural parts of its molecule. Besides hormonally active iodinated thyronines, considerable quantitites of monoiodotyrosine and diiodotyrosine, which are the direct predecessors of thyroxin, are included in the composition of thyroglobulin

Until the end of the forties, the general opinion was that iodine in the thyroid gland is found bound to the thyroglobulin molecule or in a free state in the form of iodide. The presence of free thyroxin in the nonhydrolyzed extract of the thyroid gland, was shown in 1949 by Leblond and Gross /330, 331/

Free diiodotyrosine and monoiodotyrosine were also found in the gland /579/. All these amino acids are maintained in the thyroglobulin molecule in a peptide bond and, as was shown by De Robertis /263/, free amino acids are formed from thyroglobulin during its proteolytic dissociation

The low content of iodine compounds in the nonproteinic components does not at all signify that the fraction of iodinated amino acids in the thyroid gland lacks physiological importance. These amino acids are in reality the source of thyroxin of the plasma, i.e., completed hormones, which are on their way to the blood stream. Gross and Leblond /331/ brought further proof to sustain this opinion by *way of studying* the appearance of labeled amino acids of the thyroid gland and the plasma, at various intervals of time after the administration of radioactive iodine

differs from thyroxin in that it contains ethylamine in the lateral bond instead of an alanine residue. This compound was already earlier, on the basis of pharmacological tests, presumed to be a hormone acting at the cellular level. But this opinion of Thibault was not confirmed and this is why it is at present difficult to judge the physiological importance as well as the manner of formation of this compound.



Thyroxamine

Besides, reports have also been published on the discovery of a series of unidentified spots on the chromatograms of thyroid gland hydrolysates. Hungarian scientists /293, 294/ have recently reported the discovery of a new, not yet precisely determined, iodinated compound in the thyroid gland, after administration of KI^{131}. According to preliminary results, this compound, called substance 3, contains bound acetic acid and has the faculty of stimulating respiration directly.

Thus, the extent of our knowledge on the hormonal secretion of the thyroid gland leads to the thought, that, like the sexual and the adrenal glands, this gland secretes several biologically-active products having a qualitatively homogeneous action

6. The Biosynthesis of Hormones in the Thyroid Gland

The atoms of elementary iodine, formed in the thyroid gland during the oxidation of iodides captured from the blood stream, immediately unite with thyroglobulin. In the first stage, iodotyrosines are synthesized in the gland and they appear already after 15 sec, not only in the composition of thyroglobulin, but also in the form of free amino acids. Iodotyrosines account for the basic part of activity of the gland hydrolysate, a very short time after the administration of radioiodine.

The iodotyrosines which form immediately after the absorption of radioiodine serve later on in their combined form in thyroglobulin, as well as in the form of free amino acids, for the synthesis of iodinated thyronines, which appear in the blood only after 18-24 hrs. As the activity of the iodinated thyronines in the gland rises, the quantity of iodotyrosines diminishes gradually, consequently, their genetic relationship cannot be doubted.

According to contemporary opinions, the iodination of thyroglobulin includes at least two processes on the one hand, the synthesis of iodotyrosines which includes the iodination of histidine, and on the other hand, condensation of two molecules of iodotyrosines, with the formation of thyroxin and triiodothyronines. Processes of monoiodotyrosine and diiodotyrosine deiodination also take place in the thyroid gland; these are probably formed in excess and are not used at a given moment for the synthesis of iodinated thyronines.

Formation of iodotyrosines

In the presence of an iodine molecule solutions of tyrosine and histidine may become very speedily iodinated by replacement of a hydrogen atom by an iodine atom in the ring: $RH + I_2 \rightarrow RI + HI$.

In the pure thyroglobulin Berson (cit. from Jende, /367/) discovered 0.21% of thyroxin and only 0.05% of triiodothyronine. L-3, 5, 3'-triiodothyronine is also found among the free amino acids extracted by butanol from the homogenates of the gland and is more or less regularly contained in the plasma. The importance of this triiodinated compound is determined by its biological activity, which is 3-5 times stronger than the activity of the tetraiodinated analogue.

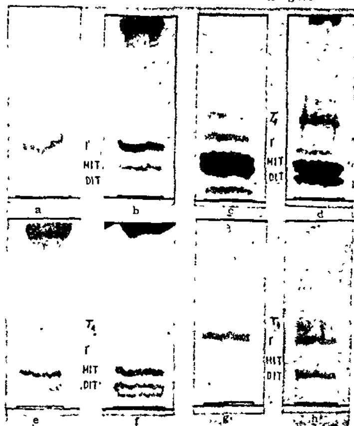
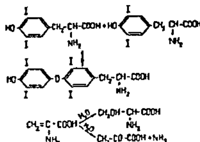


Figure 3. Radiochromatograms of butanol extracts of colloid and stroma hydrolysates of the thyroid gland of rabbits at various time intervals after administration of I^{131}

Colloid: a-15 sec, b-30 sec, c-2 hrs, d-24 hrs. Stroma: e-30 min, f-24 hrs. Butanol extract of the non-hydrolyzed thyroid gland. g-2 hrs, h-24 hrs

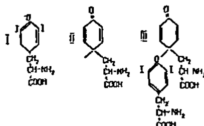
The question of the possible presence of other iodinated thyronines, identical to other compounds at least on the radiochromatograms, arose naturally in relation to the separation of 3, 5, 3'-triiodothyronine. Two substances of this nature, namely 1-3, 3', 5'-triiodothyronine and 3, 3'-diiodothyronine, were discovered by the group of Roche and Michel. The first is an isomer, according to its place, of the previously known 1-3, 5, 3'-triiodothyronine, and the other has two atoms of iodine in two phenol rings of thyroxin and is 1-3, 3'-diiodothyronine. L-3, 3', 5'-triiodothyronine was found to be almost totally lacking in antigoitrogenic activity, and 1-3, 3'-diiodothyronine has about 80% of the activity of thyroxin. The identification of these iodinated amino acids was confirmed by comparing their properties with those of the iodothyronines prepared synthetically.

Hillman, Keil and Taslimi /352/ very recently brought convincing proof of the presence, in the thyroid gland and in the plasma, of thyroxamine—a compound which



During this reaction, the alanine chain becomes separated in the form of dehydroalanine $CH_2 = \underset{NH_2}{C}-COOH$, which is then hydrolyzed into serine or pyruvic acid and ammonia.

In order to explain the condensation process of two diiodotyrosine molecules into one molecule of thyroxin, Johnson and Tewkesbury (cit. from: The Hormones, /358/) proposed a hypothesis based on the theory of free radicals. According to this hypothesis, the mechanism of thyroxin formation is an oxidative condensation of two molecules of diiodotyrosine through labile intermediate compounds, with loss of one side group /18/. The first stage of the supposed reaction is the oxidation of the diiodophenol ion by removal of one electron from the oxygen atom, with formation of a free radical (I). The second tyrosine molecule becomes oxidized by the loss of one electron in the para-position to the diiodophenol group, and thus a second free radical forms (II). According to the proposed hypothesis, these free radicals form in the biological system and then unite into a phenoxydienone (III).



In the presence of such a mechanism the diiodotyrosine molecules in the protein should be distributed so that they can react among themselves But in reality not all the tyrosine residues in the protein molecule are so distributed and this is why the quantity of thyroxin in thyroglobulin is always smaller than that which should be expected from the number of remaining tyrosine residues.

The formation of thyroxin in the process of the oxidative condensation of two diiodotyrosine molecules is also confirmed by the experiments of E.A. Kolli /80/, who showed an increase in the synthesis of thyroxin from diiodotyrosine in a medium containing H_2O_2, upon adding horse-radish or milk peroxidase.

The synthesis of thyroxin from molecules of diiodotyrosine was also shown in vitro by a series of other works, and the presence of aerobic conditions was always indispensable for the realization of the reaction.

The condensation process of iodotyrosine molecules with the formation of biologically active hormones is more effective than the simple reaction of the

The process of iodotyrosine formation in the presence of sufficient quantities of iodine takes place in such an order that monoiodotyrosine is the first to be synthesized, and then comes the synthesis of diiodotyrosine /484/.

Thus, as was shown by Roche, Michel, and Lissitzky, diiodotyrosine appears as a result of the iodination of monoiodotyrosine. The relationship between these iodotyrosines is determined by the quantity of iodine in the medium: the more haloid present, the more diiodotyrosine is formed The content of the less-iodinated derivative changes in inverse ratio. Iodinated histidine is formed only in the presence of excess iodine and the appearance of other iodinated acids is hardly probable. In the thyroid gland tyrosine is iodinated inside the protein molecule and the process of iodine binding in the gland consists of the inclusion of an atom of haloid in the molecule of thyroglobulin. As was noted in the preceding chapter, this process occurs very quickly and is very probably of an enzymatic character.

Upon hydrolysis of thyroglobulin by a proteolytic enzyme, considerable quantities of mono-and diiodotyrosine are liberated, together with hormonally active iodothyronines. According to the general opinion, they are not used in a free state for the synthesis of thyroxin and of triiodothyronines, but speedily liberate the iodine from their molecule in an enzymatic process. The iodine which is liberated again enters into the metabolic cycle and is used by the gland for the formation of hormones.

It should be pointed out that mono- and diiodotyrosine are easily deiodinated upon administration to healthy people. This process takes place under the action of a microsomal enzyme present in the thyroid gland, liver, and kidneys and requiring triphosphopyridine nucleotide as coenzyme /299,511/.

In relation to the presence in the salivary glands of a microsomal as well as a mitochondrial enzyme system, participating quite actively in the iodination of tyrosine, the question of the role of these glands in the metabolism of iodine was subjected to special research. According to the opinion of some scientists, intensive deiodination of iodotyrosines takes place in the salivary glands. But there is also another hypothesis, according to which the formation of monoiodotyrosine takes place in these glands twice as intensively as in the thyroid gland, and the halogenated amino acid enters the blood stream and is then incorporated into the thyroglobulin.

Formation of l- thyroxin

Since the first synthesis of thyroxin, made by Harington and Barger, 1-3, 5-diiodotyrosine was considered as being its predecessor in the thyroid gland. If we accept the existing opinion on the formation of thyroxin inside the thyroglobulin molecule, this process, in the course of the iodination of the protein, may be explained in two ways 1) by the iodination of the tyrosine residue and the partial transformation of diiodotyrosine molecules into thyroxin, and 2) by the presence of thyronine in a completed form in the protein and its iodination, with direct formation of thyroxin. The first explanation is the most probable one, as the presence of thyronine in the protein has not yet been proved, but, on the other hand, the possibility of condensation of the iodinated residues of tyrosine, which are in a bound state inside the protein molecule, raise some doubts. The general scheme of the condensation of two diiodotyrosine molecules may be represented in the following manner

hydrolysates we find it in the composition of mono- and diiodotyrosine. At this time, the inclusion of iodine into the thyroxin molecule cannot be demonstrated. The continuous process of enzymatic decomposition of thyroglobulin liberates molecules of di- and monoiodotyrosines, they penetrate into the cell and participate in the thyroxin and triiodothyronine synthesis.

The hormones formed start entering the blood stream; their surplus is included in new molecules of thyroglobulin, the synthesis of which also takes place continuously in the epithelial cells. Free mono- and diiodotyrosines, which are not used in the synthesis of thyroxin, are again included in the protein molecules.

Thus, according to our opinion, the condensation of two molecules of iodinated amino acids does not take place on the thyroglobulin, but from free mono- and diiodotyrosines, the thyroxin and triiodothyronine formed immediately enter the blood stream, and their surplus accumulates in combination with the protein in the colloid, in the composition of thyroglobulin they constitute a completed reserve-hormone and will be liberated according to physiological needs.

The process of hormone synthesis thus takes place inside the epithelial cells and is controlled by the thyrotropic function of the pituitary

The formation of the hormones of the thyroid gland by condensation of two molecules of iodinated tyrosine is a much more precise and reliable process and this reaction demands special mechanisms. These conditions, in our opinion, do not exist in the amorphous mass of the colloid, but are in the special structures of the follicular epithelium. The process of hormone synthesis in the cells is accompanied by the appearance of radioactivity in the follicular epithelium. It is observed as soon as two hours after the administration of radioactive iodine, and from then on it is possible to prove the appearance of small quantities of thyroxin in the gland hydrolysates by the radiochromatographic method.

In our research with administration of radioiodine to rabbits it was determined by the autoradiographic method that activity appeared in the colloid after 15-30 sec and its intensity increased from 20 min to 2 hrs after the moment of administration. During this period the radiochromatograms of the thyroid gland hydrolysates show the presence of only mono- and diiodotyrosine. Thyroxin is absent from the blood and is found in traces in the gland hydrolysates. Well defined activity in the cells appears only after 4-6 hrs and, at this time, it is already possible to determine the presence of free iodinated compounds as well as considerable quantities of thyroxin in the thyroid gland hydrolysate After 24 hrs the process of hormone formation goes on at full speed. Autoradiograms of the gland show an almost identical distribution of activity inside the cells and in the colloid. At the same time, we also discover thyroxin in the plasma.

Thus, the appearance of activity in the cells after administration of radioactive iodine does not only point to a secretion of hormones into the circulation, but also to an intensive process of iodothyronine formation.

Formation of triiodothyronines and diiodothyronine

The question of the formation of di- and triiodinated derivatives of thyronine is the most disputed one in the biochemistry of the hormones of the thyroid gland.

According to Harington and Barger, triiodothyronine appears during the action of iodine on 3, 5-diiodothyronine, and its formation is an intermediate stage in the synthesis of thyroxin. It is difficult to believe that this is precisely what takes place in the gland For actually, on the one hand, the condensation of

iodination of the protein molecule, and it is probably controlled by the thyrotropic hormone. This is shown by the results of studies on the synthesis of the thyroid hormones in hypophysectomized rats. Morton et al. /429/ reported that after hypophysectomy, together with a sharp reduction of the accumulation of iodine in the thyroid gland, the coupling process of iodotyrosine molecules into thyroxin also becomes disordered. The realization of the oxidation process of iodide into elementary iodine and the formation of diiodotyrosine in the thyroid gland are not diminished, but the synthesis of thyroxin is found to be strongly limited, which is shown by the considerable reduction of its quantity in the plasma.

Thus, the views generally accepted today on the synthesis of thyroxin and triiodothyronines are based on the prerequisite of the realization of this process inside the protein molecule. Consequently, iodide, upon passing through the epithelial cells of the follicles, is oxidized into elementary iodine and included in the thyroglobulin molecule, forming mono- and diiodotyrosines. The following process should be the synthesis of iodinated thyronines, which is supposed to occur through the condensation of two iodotyrosine molecules which are already in a peptide bond in the composition of the protein, or the presence of a thyronine structure in the molecule of thyroglobulin—and in this case it is simply iodinated. Both these possibilities are not directly confirmed by experiments, but are accepted by scientists, possibly because no other more satisfactory scientific explanation exists.

But, in our opinion, both of these possibilities seem too hypothetical.

For the first proposed reaction to occur it is indispensable to accept an interaction between the iodinated tyrosine residues, which are in a stable chemical bond in the peptide chain of the protein molecule. The difficulty of such a reaction is evident. The above interaction would probably be unique, even in the awkward case of the synthesis of a relatively simple molecule, which should then be liberated from the big proteinic particle by enzymatic disruption of the peptide chain.

The acceptance of the second supposition demands, as an indispensable condition, the presence of a completed thyronine structure in thyroglobulin, which it was not possible to confirm even with the most perfect methods of chemical analysis. There are evidently no thyronine molecules in the composition of thyroglobulin. From the point of logical considerations, there is yet another considerable [illegible] of thyroxin formation in the thyro- [illegible]

and they must then become deiodinated or again included in the thyroglobulin molecule. We thus obtain a completely useless iodine cycle inside the thyroid gland, as the iodotyrosines do not have hormonal activity and do not penetrate into the blood and in a free state they are not used for the synthesis of thyroid hormones. It seems to us that such unproductive activity does not coincide with the activity of biological systems.

We recently took up the study of this question and another point of view on the general development of hormone formation in the thyroid gland arose on the basis of some experimental results we obtained /144, 149/.

In our opinion, this process takes place in the following manner. The iodide which is absorbed by the thyroid gland, after oxidation and the formation of elementary iodine, *is immediately included into* the composition of thyroglobulin in the form of mono- and diiodotyrosine. In this form it accumulates and is retained in the colloid, constituting the iodine reserve of the gland. Both appearing iodotyrosines are thus the predecessors of the thyroid hormones. During this period, we discover iodine in the colloid on autoradiograms; on radiochromatograms of thyroid gland

7. The Secretion of Hormones by the Thyroid Gland

As follows from the above-mentioned, it may be accepted that the hormones of the thyroid gland are formed in the cells, as condensation products of iodotyrosines, as well as in the colloid of the follicles, where it occurs in the process of thyroglobulin proteolysis. Thyroglobulin, synthesized in the epithelial cells, accumulates in the follicles and remains there temporarily as a reserve product containing iodinated thyronines in a bound state. According to the extent of demand for the hormone by the organism, thyroglobulin becomes dissociated and the iodinated amino acids enter the blood or lymphatic circulation. Thus, the biological importance of thyroglobulin is that it contains all four iodinated derivatives of thyronine, which constitute the hormonal secretion of the thyroid gland. In some cases, as for example during the augmentation of hormone secretion under the action of the thyrotropic secretion of the pituitary, the dissociation of the iodinated protein globules also takes place intracellularly. Colloid may keep on forming even if the administration of iodine is blocked by goitrogenic agents. When iodinated thyronines form in the cells, the product is secreted into the lumen of the follicles only after hormone formation is completed.

As was proved by Dougherty et al. /273/, hormone formation in the thyroid gland is a continuous process, the entrance of inorganic iodine into the gland and *its liberation in the form of hormonal iodine occurs at the same rate* Consequently, only completed hormones enter the circulation and iodinated tyrosines do not enter it.

Notwithstanding the sequence and the logical nature of this explanation, the problem of the secretion of thyroid hormones from the gland into the blood stream has a number of unclarified aspects. In what manner do the hormonally active iodinated amino acids enter the blood stream, why do mono- and diiodotyrosine not enter the circulation, how, during increased functioning of the gland, do droplets of thyroglobulin penetrate into the epithelial cells and how does its proteolysis take place under these conditions, and finally, does the secretion of the hormone take place through the cells of the follicular epithelium or through the intercellular spaces? All these questions still remain open for the time being

A proteolytic enzyme, discovered by De Robertis, capable of liberating iodinated amino acids from thyroglobulin, was recently isolated from the thyroid gland and purified /479/.

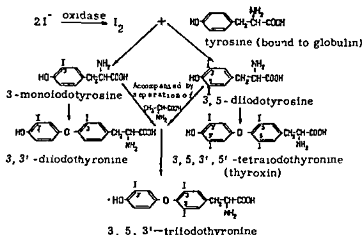
The absence of any perceptible quantities of diiodotyrosine and monoiodotyrosine in the plasma of healthy and thyrotoxic people is caused, in our opinion, mainly by their being utilized in the synthesis of iodinated thyronines, but depends also on the inclusion of these compounds in new molecules of thyroglobulin synthesized by the cells, and on their partial destruction in the tissue of the thyroid gland No proof has yet been brought that they do not pass into the circulation through the cellular wall as easily as hormonally active iodothyronines.

It is unlikely that the absence of iodinated tyrosines in the blood stream is caused by their low penetrating properties. It should be sooner accepted that they do not accumulate in the free state in perceptible quantities as a result of their speedy utilization in the epithelial cells.

The discovery of a deiodinating enzyme ensuring the separation of iodine from the molecules of mono- and diiodotyrosine speaks for the possibility of a deiodination process in the tissue of the thyroid gland. This enzyme also removes the atoms of the haloid from bromide derivatives of tyrosine, but does not act on thyroxin and triiodothyronine.

l-*tyrosine with* l- 3, 5-*diiodotyrosine is unlikely*, and on the other hand, recent chemical research on the iodination of thyronine and its mono- and diiodinated derivatives raised the possibility of another method of the halogenation of this amino acid

The biosynthesis of triiodothyronine and 3, 3'-diiodothyronine in the thyroid gland may be the result of the condensation *of two molecules of iodotyrosines, or* of a partial deiodination of products more rich in iodine, thyroxin being among these. The first of these reactions could take place according to one of the following schemes and would lead to the formation of all three iodinated thyronines, as this also takes place during the synthesis of thyroxin from two molecules of diiodotyrosine.



In these reactions the formation of iodinated thyronines is not at all linked to any deiodination process. And actually, it has not been possible up to now to show the deiodination of thyroxin or of its less halogenated homologues, which might lead to the formation of other biologically active derivatives. Such a deiodination process in the thyroid gland has been proved for l-monoiodotyrosine and l-diiodotyrosine, it is known that this process takes place with the participation of a special enzyme, which was found to be ineffective in the deiodination of thyroxin or triiodothyronine. But there is a considerable number of reports in the scientific literature on the deiodination of thyroxin in other organs and tissues of the organism. This leads to the question: is not the formation of tri- and diiodothyronines at the expense of the free l-thyroxin in the receptive cells an even more important *process in the physiological sense? This is already related to the field of* the metabolism of the thyroid gland hormones and will be dealt with in Chapter IV.

Thus, the biosynthesis of all the hormonal products secreted by the thyroid gland into the circulation should be considered today as the result of the condensation of two iodotyrosine molecules. Consequently, the synthesis of all the derivatives of thyronine in the thyroid gland is effected by one common mechanism.

halflife of radioactive iodine in the gland, which is composed of the physical half-life as well as the rate of the metabolic cycle of iodine in the organ. Rosenberg /503/determined this value after administering 50μC of I^{131}, by measuring absorption after 24 hours in the region of the neck and then measuring the drop of radioactivity on the hip until equilibrium with the background set in. The calculation formula was as follows: =

biological half-life period =

$$= \frac{(\text{reading on the neck} - \text{background or reading on the hip}) \times \text{factor of physical decay}}{\text{administered dose}}$$

The biological halflife of the metabolic transformation of radioactive iodine in a normal human thyroid gland is equal to about 10 days, according to the results of various authors, but it undergoes considerable fluctuations. Thus, Rosenberg, upon studying 98 healthy men aged from 22 to 83 years, found the range of the biological halflife to be from 21 to 200 days.

All the above-mentioned stages of intrathyroidal transformation of iodine are thus summed up in the fact that the inorganic iodine which enters the thyroid gland continuously returns to the circulation in the form of hormonally active compounds, which are later metabolized in the organs and tissues in the process of their physiological action.

But, under physiological conditions, the process of deiodination of monoiodotyrosine and diiodotyrosine cannot reach considerable extents, and thus does not play a considerable role in the iodine metabolism of the thyroid gland itself or that of other tissues. Apart from this, if we accept the existing concept on the important role of the deiodination processes in the epithelial cells and in the formation of iodinated compounds inside the protein molecule, the thyroxin content of thyroglobulin should be considerably larger than that shown by precise chemical analysis, and inorganic iodine should be contained in noticeably greater quantities in the cells than in the colloid, in view of the deiodination processes which constantly occur in the cells.

The hormonal secretion of the thyroid gland is under the regulating influence of the pituitary. Sterling and his group /549/ showed that by blocking thyroidal reutilization of I^{131} with 1-methyl-2-mercaptoimidazole the augmentation of the rate of loss of thyroidal I^{131}, after the administration of thyrotropic hormone, may be caused by the augmented hormonal secretion rate, independent of any influence on the accumulation process of iodine or on the synthesis of the hormone. In a recent research by Dobyns and Hirsch /267/, in experiments on dogs with the use of I^{131}, it was shown that there is an increase in total radioactivity, as well as in the content of protein-bound iodine in the lymph of the lymphatic vessel situated near the thyroid gland, after the administration of thyrotropic hormone. But radiochromatographic determination of the iodine-containing fractions showed a basic activity in one unchanging compound, which is in all probability thyroglobulin. Thyroxin and iodide were not found in the lymph. The thyrotropic hormone increased the passage of I^{131} compounds into the vein of the thyroid gland. On the basis of tentative calculations, the authors expressed the opinion that, during thyrotropic stimulation, the lymph is a more important passage for the exit of I^{131} from the thyroid gland than blood.

The problem of the thyrotropic regulation of the functions of the thyroid gland was studied in detail from the morphological and physiological aspects by Russian scholars and a light is thrown on it in a series of experimental communications and surveys (Aleshin, /6/; Eskin, /173/; Tonkikh, /140, 141/; Genes, /39/). The question will be examined in a more detailed manner in Chapter VII.

The rate of thyroid gland hormone secretion was studied by various methods, on several types of animals and on man. It was established that the rates of entry and exit of hormonal iodine are constant and equal. The rate of I^{131} secretion by the thyroid gland was measured by the loss of this isotope from the gland, after administration of topazole which prevents reabsorption of I^{131}, and also by the kinetics of thyroidal I^{131} distribution in the extrathyroidal pool, before administration of topazole. Both methods gave identical values, reaching about 10% of the total daily thyroidal ioidine in thyrotoxic subjects. It was established by various methods that euthyroidal subjects secrete daily 115-120 μg of organically bound iodine.

Analogous research was made in the laboratory of Ya. M. Kabak by A.E. Rabkina /115/, who totally suppressed hormone formation in the thyroid gland of rats by administering methylthiouracil, and determined the necessary dose of thyroxin which prevents the development of the goiter reaction. This quantity, which equals 6-7 μg in winter and 4 μg in summer, corresponds to the daily hormone production by the rats.

The secretion rate of the thyroid gland is also represented by the biological

with the degradation of the side chain of the molecules, from the deiodinated compound besides monoiodotyrosine and an iodine ion.

As has been noted before, the capacity of deiodinating iodotyrosines is reduced in persons suffering from a particular form of congenital defect of the iodine metabolism /299/ This uncommon disorder of iodine metabolism is observed in cases of a combination of sporadic cretinism and goiter

The metabolism of the thyroid hormones has general aspects, concerning their distribution and degradation in the whole organism; these questions can also be examined from the aspect of metabolic particularities in the various tissues, especially in relation to intrahepatic transformations. The first aspect includes problems of thyroid hormone circulation, their intracellular degradation, and the excretion of the metabolic end products The second complex of questions touches upon the metabolism of the thyroid gland hormones in different tissues, mostly in the hepatic cells and in the tissues of the brain

1 Distribution and Rate of Total Degradation of the Thyroid Hormones

The metabolism of the thyroid gland hormones was studied either by the administration of exogenously I^{131}-labeled thyroxin and triiodothyronine, or by observing the distribution and degradation of endogenously labeled iodothyronines after administration of radioactive iodine It should be taken into account that, during exogenous labeling, thyroxin and triiodothyronine usually contain I^{131} in the positions 3',5', which are more labile than labeling in the positions 3,5/494/. This is why comparison of the results of research made with synthetic or with biosynthetic labeled hormones should not be made. Thus, for example, Myant and Pochin (cit from Berson/214/) noted a speedier disappearance from the plasma of synthetic l-or d-thyroxin (labeled in positions 3',5') than the excretion of plasma hormone, labeled in vivo This was also observed by Sterling and his co-workers /549/

Upon injecting small quantities of dl-thyroxin intravenously, its concentration in the plasma is lowered relatively slowly This reduction depends on the establishment of an equilibrium with the peripheral tissues The volume of thyroxin distribution, relative to its content in the plasma, may be defined by determining the concentration of I^{131}-thyroxin remaining in the plasma when equilibrium is established It was seen by this way that, in euthyroidal subjects weighing 70 kg, thyroxin becomes distributed in a volume of 23 liters, which constitutes 32 6% of the body weight/178/ After total establishment of equilibrium thyroxin disappears from the blood stream at a rate of about 11% daily. Triiodothyronine disappears more swiftly from the blood, at an average rate of 27.4% daily The disappearance of the labile hormone in patients suffering from thyrotoxicosis is considerably faster than in euthyroidal ones, and constitutes 22% daily, while in hypothyroidal patients it is only 9 8%/216/

The biosynthetic hormone becomes metabolized somewhat faster than the exogenously administered hormone, in connection with the fact that it contains, besides thyroxin, a certain quantity of triiodothyronine. Upon administering physiological doses (in μg) of labeled thyroxin or triiodothyronine to rats, some organs become richer than others in radioactive substances, but the greater part of activity is speedily excreted in urine in the form of iodides, which points to the degradation of the administered iodine compounds The quantitative aspects of this degradation are very important for pathology and for experiments, as they permit the evaluation of the daily demand of the organism for thyroxine or hormonal iodine

The metabolic rate is also evaluated by the clearance from the plasma of an endogenously labeled hormone/216/ through preliminary administration of I^{131}; during this, urinary excretion of I^{131} was taken into account, after blocking repeated utilization of it in the thyroid gland by antithyroidal substances The rate of

Chapter IV

THE POSTTHYROIDAL METABOLISM OF HORMONAL IODINE

(Posttireoidnyi Metabolizm Gormonal'nogo Ioda)

The postthyroidal metabolism of iodine concerns hormonal iodine after its secretion from the thyroid gland The thyroid hormones which enter the circulation are carried by the blood stream to all parts of the organism and are distributed in its tissues, where they are subjected to various chemical transformations and reconversions These processes take place before or after partial or total deiodination of the halogenated thyronines If, up to recent times, our knowledge on this question touched only upon thyroxin, the last years have seen the appearance of an especially great interest in other thyroid hormones, their natural presence in the blood and in various organs, and their tissue metabolism The second most important hormone of the thyroid gland—3, 5, 3'-triiodothyronine—was especially studied

We have rather detailed information on the metabolism of these two basic thyroid hormones, yet even in this case not all the problems created by the metabolism of the hormonal amino acids have been solved

As to other iodothyronines, as for example 3, 3'—diiodothyronine and 3,3',5' -triiodothyronine, recently discovered, the study of their metabolism, which has been made very recently, put in doubt their physiological role in the organism.

As was shown by Stanbury and Morris/541/, and Dunn and Stanbury/279/, who injected I^{131}-labeled diiodothyronine and 3,3',5'-triiodothyronine intravenously to euthyroid persons, these components become so speedily deiodinated and excreted from the organism, that their role among the natural hormones of the thyroid gland seems improbable According to the opinion of the above authors, if both these substances form in the same manner as iodotyrosines, they become degraded in the gland or are used as predecessors for hormone production

The metabolism of monoiodotyrosine and diiodotyrosines were also studied after administration of I^{131}-labeled iodotyrosine to the organism The distribution and excretion of the diiodotyrosine iodine corresponds almost fully to the behavior of the radioactive iodide administered to the organism. Experiments with physiological amounts of diiodotyrosine /370/revealed its quick degradation and excretion from the organism in the form of iodides L-monoiodotyrosine and diiodotyrosine are speedily deiodinated upon administration into the organism. This process is related to the activity of the microsomal enzymatic system, which exists in the liver, kidneys, and thyroid gland, and demands triphosphopyridine nucleotide as a cofactor. As was determined in studies by Ruegamer and Chodos /511/, the greatest concentration of this enzyme is noted in the liver and kidneys There was no synergism noted between the thyroid gland and the salivary glands in the deiodination of iodotyrosines /510/ According to the results of Roche, Lissitzky,and Benevent /480/, liver sections deiodinated more monoiodotyrosine than diiodotyrosine and during this process yet another series of products is formed,

patients suffering from hypertension or from cancer of the thyroid gland after having given them radioactive iodine.

Reports have been published on the appearance of abnormal iodinated compounds in the blood, or of the exit of thyroglobulin from the gland, in some diseases of the thyroid gland These cases will be examined in chapter IX.

Thus, there is no longer any doubt about the fact that thyroxin is the basic peripheral hormone of the thyroid gland. The appearance of 3,5,3'-triiodothyronine in the blood is also not disputed But the presence of 3,3'-diiodothyronine and 3,3,5'-triiodothyronine in the circulation, at least in man, is not generally accepted. The appearance of the remaining iodinated compounds is related to pathological processes in the tissues of the gland.

It was recently shown that thyroxin enters into the composition of erythrocytes, but its concentration there is only 25% of the concentration in the plasma

It has been known for some time that thyroxin in the blood is found bound to the protein It does not separate during dialysis and precipitates together with the plasma proteins, under the action of various protein precipitators. Some of these reagents, as for example trichloroacetic acid, denature the proteins in an acidi medium, in which thyroxin liberated from the protein is practically insoluble Other reagents, as for example the hydroxides of metals, adsorb proteinic compounds of thyroxin Normal butyl alcohol extracts almost all the iodine from the plasma The iodine extracted from the plasma constitutes the iodine of thyroxin and of small quantities of triiodothyronine, the latter closely resembles thyroxin by its solubility in butanol. During the treatment of plasma by butyl alcohol, disruption of the weak bond between iodine and protein takes place in such a way that all the iodine bound to the protein, as well as small quantities of the free iodine of thyroxin and triiodothyronine pass into the extract.

Whereas iodide is equally distributed between the plasma and erythrocytes, protein-bound iodine is found only in the plasma. This is why some authors/256/ propose the use of the iodine ratio $\frac{\text{erythrocytes}}{\text{plasma}}$ as an indicator of hormone formation

The quantity of protein-bound iodine (PBI of the blood), in a normal man, is 4-8 μg per 100 ml of blood Its presence is a rather reliable indicator of the thyroid hormones circulating in the blood Although the fact of the binding of thyroxin to protein of the plasma is not doubted, the nature of the thyroxin-binding protein (TBP) has not yet been definitively cleared up

During the last years, the question of the form of thyroxin transportation in the blood was intensively studied Older studies attempting to clarify the nature of the TBP by way of saline precipitation or by electrophoretic separation, showed the distribution of iodine between albumins and α- and β-globulins The method of paper electrophoresis of the plasma of patients receiving iodine, has recently been used with great success The research of Gordon and others /324/, using this method, made it possible to localize at pH = 8 6, the I^{131} of the plasma together with a protein having a mobility analogous to that of an α-globulin Labeled thyroxin added to the plasma also moved mostly to this position But a small part of the radioactivity was also found in the albumin fractions

Later works in this field/258/ showed that the TBP moves at pH = 8 6 to a position between the α_1- and α_2-globulins, a similar mobility was discovered for the TBP also at pH = 7 6-6

Notions thus arose about a special protein fraction of the serum which

metabolism is also. evaluated in the absence of such a block, by urinary excretion and the accumulated I^{131} $\frac{\text{thyroid gland}}{\text{urine}}$

Upon determining the metabolic rate of the thyroid hormones, the general metabolism should also be taken into account; this is why the biological halflife of the thyroid hormones cannot be examined without paying attention to the level of metabolism Riggs/472/evaluated the daily utilization rate of the hormone from the results of protein-bound iodine concentration at various metabolic levels, and showed that, with the augmentation of the concentration of the plasma hormone, the speed of its utilization also rises. His results, as well as those obtained by Berson and Yalow/216/, made it possible to propose a formula by which it is possible to evaluate the quantity of hormonal iodine utilized by man This formula is as follows. $D = 2\ 9\ (PBI)^2$, where D = μg of hormonal iodine degraded daily and PBI = μg of iodine bound to the protein, in 100 ml of plasma It follows that the metabolic rate of the hormones is proportional to the protein-bound iodine of the plasma The demand for hormones of the thyroid gland was found to be somewhat lower than the total quantity of thyroxin secreted by the gland, for thyroidectomized rats were found to have a normal basal metabolism upon receiving only 0 6 μg of 1-thyroxin per 100 g of body weight, while Albert and Keating/178/evaluated the daily secretion of thyroid hormones in a normal rat to be 3-8 μg

2 The Fate of the Thyroid Gland Hormones in the Blood Stream

Many years passed after the discovery of thyroxin before it became possible to study in great detail the nature of the thyroid hormones circulating in the blood Thyroxin itself is considered to be the main hormonal product, but the prolonged latent period between the time of its administration and the appearance of signs of its action, and also the difference between the activity of thyroxin and the effect obtained by administration of the total substance of the thyroid gland, raised doubts as to the fact that it is the veritable peripheral hormone of the thyroid gland

Some researchers thought that thyroglobulin may also be a circulating form of the hormone, but Lerman (cit from· The Hormones /358/) showed in 1940 by the immunochemical method that it is absent from the blood

Most convincing proofs of the fact that thyroxin itself is the hormone circulating in the blood, were obtained by Taurog and Chaikoff/565/.

The use of chromatographic analysis, together with administration of I^{131}, opened new possibilities for the study of the composition of the iodine-containing compounds in the blood On the basis of contemporary results, it should be thought that, from the physiological point of view, the hormone of the thyroid gland is a mixture of 1-thyroxin, 1-3,5,3'-triiodothyronine, 1-3,3',5'-triiodothyronine and 1-3,3'-diiodothyronine. These products contain at least 90% of the total iodine in the plasma. In this mixture, thyroxin prevails, constituting 3/4, and sometimes even more of the total quantity of organic iodine of the plasma 1-3,5,3' and 1-3,3',5'-triiodothyronines are found in traces, and the quantity of 1-3,3'-diiodothyronine, according to the results of Roche and Michel, may reach 25%/500/.

Under normal conditions, monoiodotyrosine and diiodotyrosine do not enter the blood, but they were discovered in some pathological states Both of these compounds are inert from the physiological point of view

Thyroglobulin was found in the blood, only as a result of traumatic changes of the thyroid gland This protein appears in the blood in minimal quantities after surgical traumas. Robbins and others/476/found thyroglobulin in the serum of

highly active protein, moving within the alpha zone.

In previous research preliminary deductions were made according to which the TBP, at pH = 4, has an analogous behavior in electrophoretic mobility, isoelectric point, and constant of sedimentation in the ultracentrifuge with the α_2-glucoproteins of Schmidt /520, 521/, or is identical to the M-2 glucoprotein (mucoprotein). But Peterman's group/476/ assumed that the TBP cannot be a mucoprotein, in view of its electrophoretic activity at pH = 4 5 and of the fact that the mucoproteins of human serum have a high level in hyperthyroidism and a low one in myxedema But no differences were discovered in the binding of thyroxin by the serum of euthyroidal and hyperthyroidal patients, and Ingbar/362/ noted that mucoproteins prepared by the method of Meil and others do not have the property of binding thyroxin

Study of the thyroxin-binding protein showed that its molecular weight is about 50,000, if it has a dissociation similar to that of albumins Its electrophoretic mobility, at pH = 4 5, is of special interest, at this pH value the albumin is at the isoelectric point and only small quantities of globulin are negatively charged

Summarizing all that has been said on the nature of the TBP, it may be said that it is an α-globulin which is found in very small quantities in the serum Its isoelectric point is lower than 4.5, and it may be a glucoprotein Under physiological concentrations of thyroxin, it binds the greater part of this hormone found in the serum

The problem of the chemical nature of the point of binding of thyroxin to the protein remains as yet unsolved. Some results on this problem were obtained upon studying the relative binding force, after effecting changes in the thyroxin molecule It is possible to approach the question of the binding of thyroxin analogues also by the analysis of the excretion of I^{131}-labeled hormones, after administering them to the blood in corresponding quantities This excretion will possibly show the saturation of the TBP by thyroxin Various types of animals exhibit a great variety of reactions of the TBP with thyroxin

The limits of binding thyroxin with the TBP in the serum change during pregnancy and in a series of pathological states For example, the binding capacity is lower than normal in nephrosis, higher in hyperthyroidism and pregnancy, and does not change in hypothyroidism

Another highly active thyroxin-binding protein was recently discovered in the course of isolation of protein fractions of the human serum, gradually enriched by the TBP It could be discovered by a characteristic mobility during electrophoresis in a veronal buffer at pH = 8 6, it moves in the direction of the anode, about 20% faster than serum albumin This prealbumin was also isolated, apparently in a pure form, and was found to have an especially high affinity for thyroxin

The binding of thyroxin by proteins, moving in front of albumin in the course of electrophoresis in a veronal buffer, was already reported for the cerebrospinal fluid and serum of normal and nephritic patients/497/, but its importance was not perceived When serum containing labeled thyroxin and complemented by an increasing quantity of stable thyroxin is subjected to electrophoresis, it is noted that the quantity of hormone associated to the prealbumin is very high when the latter is in low concentration and capable of being bound to the TBP. Saturation of the TBP is completed when 25 μg of thyroxin are bound to the protein of 100 ml normal serum while at the same time prealbumin has the capacity of binding about 100 μg thyroxin per 1,000 ml of normal serum Triiodothyronine, in contrast to thyroxin, is almost not bound at all to the prealbumin when added to the serum A series of proofs and considerations were brought on the fact that the prealbumin is really an independent fraction, having the characteristic of becoming associated with thyroxin in veronal

predominately binds endogenously formed or exogenously administered thyroxin But it was soon determined that, although the greater part of the concentration of the labeled thyroxin indicator became associated with the TBP, greater quantities of it became bound to the albumin as the concentration of thyroxin grew This led to the assumption that TBP and albumin are, respectively, the initial and the secondary carrier of thyroxin. The distribution of labeled thyroxin between the TBP and the albumin of the serum, in the fractions of which the quantity of stable thyroxin existing in the blood was contained, was used as a means for determining the relative capacity for thyroxin binding by the TBP under normal and abnormal conditions /274/

In euthyroid persons, the capacity of the TBP to combine with thyroxin is limited to about 0.4 μg of thyroxin per ml of blood Other authors observed the continued increase of thyroxin bound to the α -globulin fraction. This quantity does not remain constant, and changes depending on time and dose According to Horst, Freinkel, and others (cit. from Pitt-Rivers/457/), the free thyroxin of the serum remains in a labile form in inverse ratio to the TBP and albumin. The passage of thyroxin from albumin to the TBP may take place during a decrease of the thyroxin concentration or during an increase in the binding capacity of the protein Robbins and Rall/478/ showed that the quantity of thyroxin bound to the protein rises as a linear function upon adding thyroxin to the serum, until it reaches a concentration of about 0 1 μM Further addition of thyroxin leads to a curved line, which is considered as being the saturation of the TBP and the transfer of the hormone to other protein fractions The authors found that such saturation takes place when the concentration of thyroxin in the blood is 2-3 times above its normal level The binding of thyroxin with these proteins is stable to a certain extent, although the bond is not strong and probably has an adsorptional character. This association is destroyed by the action of various denaturing reagents, which dialyze thyroxin while it is not dialyzed in the plasma in vitro

The multiplicity of the thyroid hormones leads to the question of which of the thyroid gland hormones become bound to the blood The TBP mostly binds thyroxin of the serum It is as if this protein can separate thyroxin in a mixture from other iodinated amino acids

Triiodothyronine is also bound to the proteins of the blood, although its bond is somewhat weaker Its behavior in the blood is in sharp contrast to that of l- thyroxin. The compounds of l- triiodothyronine with the blood proteins are mainly with globulin glucoproteins and they are considerably weaker than the l- thyroxin compounds in the same fractions in vivo/457/ This phenomenon is of great physiological importance, it explains the very small triiodothyronine content of the blood, nothwithstanding its continuous secretion from the thyroid gland The iodine of triiodothyronine sometimes corresponds to 10-15% of the l-thyroxin iodine of the gland, while under the same conditions, it is never higher than a few hundredths of a percent of the total iodine of the plasma. In rats the plasma sometimes totally lacks this compound as the triiodinated derivatives diffuse more easily than l-thyroxin, and it may be that it disappears sooner from the plasma. In order to test this assumption research was made on the rate of reduction of the concentration of these compounds in the blood after the administration of physiological doses of both hormones to rats The binding of triiodothyronine with various proteinic fractions of the serum in vitro was studied by Dingledine, Pitt-Rivers, and Stanbury/266/. The basic carrier of triiodothyronine was the TBP, but it was also associated with albumin and with the globulin fractions, although the concentration in them was low—1 2 μg%.

Much effort was made in order to clear up the physical, chemical, and physiological properties of the TBP. Very recently, Ingbar/362/succeeded in isolating, by electrophoresis and sedimentation, a homogeneous preparation of a

during proteolysis of the protein inside the thyroid gland. But is this their only origin? *Is it not possible to think that one of these fractions is formed by partial* deiodination, in the receptors of hormones richer in iodine? As to l-3,5,3'-triiodothyronine and l-3,3',5'-triiodothyronine, this question is disputable Various opinions exist in scientific literature Some authors believe in the formation of triiodothyronines in the tissues during the degradation of thyroxin, others refute this belief. The peripheral formation of l-3,3'-diiodothyronine may be considered certain Its origin is in the cells and it is produced at the expense of l-thyroxin and l-3,5,3'-triiodothyronine, but it is hardly probable that it passes from the tissues into the plasma, for, as is shown by a series of studies, l-3,3'-diiodothyronine is speedily destroyed during the process of this formation

Thus, according to the actual state of our knowledge, it should be thought that the hormones found in the blood stream are in most cases transported from the gland to the cells. But there are facts showing that under some pathological and experimental conditions a series of particularities are observed in the metabolism and formation of iodothyronines in the tissues. Thus, for example, it is known that gluconated derivatives of triiodothyronines enter the blood during bile duct occlusion. Besides, there are reports on the presence of an unknown iodinated product (substance C) of an analogous nature after the injection of physiological doses of l-thyroxin and triiodothyronine to thyroidectomized rats. But no further reports have appeared on this component C.

3. The Metabolism of Hormonal Iodine

The rate of secretion or degradation of the thyroid gland hormones are studied by means of the secretion of I^{131}; in many cases labeled thyroxin, triiodothyronine, and other iodinated components are administered to animals and these indicators are studied under various experimental conditions. Similar observations were also made on healthy people and on patients suffering from thyrotoxicosis or hypothyroidism. These results give us an idea of several general properties of the metabolism not only of the exogenously administered hormone of the thyroid gland, but also of the endogenously produced hormone. The administration of l- thyroxin or l-3,5,3'-triiodothyronine in physiological doses (μg) to thyroidectomized rats is accompanied by the excretion of the greater part of the hormonal iodine in the urine and a smaller part in the feces Beginning with a dose of 10 μg of l- thyroxin 20-30% of the administered dose is found in the urine and 15-20% in the feces within 48 hours. When the administered dose is increased the part of the hormonal iodine excreted in the feces also increases The dominance of the excretion in feces upon administering considerable quantities of the preparations is created by the fact that during this the antagonistic processes become more important than the tissue metabolism of the hormone Upon administering large doses of thyroxin to the organism, the detoxicating mechanisms of the liver come into play. In any case, urine contains mainly iodides and feces mainly the hormonal iodine contained in thyroxin and triiodothyronine

After the injection of a small quantity of thyroxin its concentration in the plasma is slowly reduced during the first 6-12 hours and then its speed of disappearance becomes even slower. D-thyroxin disappears from the blood considerably faster than l-thyroxin Meticulous research made by Johnson and Albert/370/ on rats, upon administration of physiological quantities of radioactive iodine, I^{131}-labeled thyroxin,and diiodotyrosine showed that after the injection of radiothyroxin the activity in the animal is slowly reduced; 30% of the total dose is excreted in urine and 40% in the feces within 48 hours After administration of diiodotyrosine only 12% of activity was excreted with the feces during the first 8 hours and almost all further excretion occurred in the urine, 75 8% of the total activity was excreted in the urine within 48 hours, which points to the speedy deiodination of diiodotyrosine

buffer the presence of prealbumin is supressed *either by its combination to other* fractions or by the interaction with proteins.

Thus, together with the TBP—the basic carrier of the serum thyroxin—another new component of the protein fraction is found, which also has a *high* attraction for this hormone But the nature of both of these components and their precise physiological importance still demand further research

The level of the protein-bound iodine of the serum is used to characterize the functional state of the thyroid gland Most authors consider the normal level of PBI to be from 4 to 8 μg per 100 ml of blood, more than 8 μg in hyperthyroidism, and less than 4 μg in myxedema But there is overlapping of these values, especially around the upper limit of the normal range and the lower limit of hyperthyroidism This is why it is thought that the determination of PBI is important for diagnosis in order to differentiate between the normal and hypothyroid states but is not always justified in the differentiation between euthyroid and hyperthyroid groups.

Some authors try to use the binding of iodine with the globulin fraction for diagnosis, when the results of the PBI do not concur with the clinical picture Thus, according to the results of Winikoff/611/, the globulin fraction obtained by saline precipitation contains a small part of the PBI In view of the fact that the distri*bution of thyroxin between the various fractions of protein depend on its content in* the blood, the quantity of globulin-bound iodine may characterize the total quantity of organic iodine in the blood According to this author, the level of globulin-bound iodine is the best index differentiating between the hyper- and euthyroid groups *(respectively higher than 2 0μg% and lower than 1.7μg%). The quantity of the* iodine bound to albumin was found to be useless as an index for diagnosis of the functional state of the thyroid gland

Vannotti and Beraud/593/, studying the binding of thyroxin by blood proteins during diseases of the liver, came to the conclusion that the capacity of the TBP fraction to fix the hormone may also change under such conditions Discrepancies in the clinical picture of the PBI level in disorders of thyroid function are explained, in their opinion, by the different relation between thyroxin bound to the protein and free thyroxin, for the metabolic effect of the thyroid gland hormones is a function of free thyroxin penetrating into the cell and the level of free hormone in the serum is subjected to change, under the influence of various extrathyroidal mechanisms. Consequently, the level of PBI may in a number of cases rise without an answering reaction by the organism, *as is seen for example during pregnancy* In hyperthyroidism the quantity of free thyroxin in the serum rises considerably with the augmentation of the PBI

It is supposed that in euthyroid and hyperthyroid patients at least the quantity of metabolized thyroxin is also a function of the free thyroxin In relation to the fact that the concentration of free thyroxin in blood is very low, structures which are subject to the action of thyroxin should be extremely sensitive to the action of the hormone, or should possess a special mechanism of concentration, or should have both particularities.

We have no reason to doubt the exclusive thyroidal origin of the thyroxin circulating in the blood of man and higher vertebrates, except for possibly its minute formation in extrathyroidal gland tissue *In any case, thyroxin is not a meta*bolic product of the thyroid hormones and it is not elaborated by other tissues of the organism.

The origin of the other iodothyronines in the blood stream is not always indisputable and raises the question of extrathyroidal metabolism. These amino acids are undoubtedly an integral part of thyroglobulin and are liberated as such

General degradation of the hormonal products in the entire organism is accompanied by the return of iodine into the circulation in the form of iodides, which are then again included into the extrathyroidal pool and the general iodine cycle. Part of them is fixed by the thyroid gland and is used again for the halogenation of thyroglobulin, while the main quantity is excreted in the urine.

Thus, it is possible to observe the degradation rate of iodothyronines according to the excretion of iodides after the absorption or injections of radioiodine. In man the rate of l-thyroxin iodine excretion is relatively small, as the half-life period of the hormone after administration of therapeutic doses is 7-12 days /178, 467/. As the initial rate of disappearance of I^{131}-labeled thyroxin and triiodothyronine from the blood stream is considerably higher than their disappearance from the serum proteins, it seems evident that hormones not bound to blood proteins pass into the tissue through the capillaries The rate of the appearance of the hormone action on cells in vivo should be at least limited by the dissociation constant of the thyroxin-protein complex in the plasma and tissue:

$$K = \frac{(\text{thyroxin})\,(\text{protein})}{(\text{thyroxin-protein})}.$$

The passage of triiodothyronine from the blood into the tissues and its metabolic transformation in the organism occur faster than those of thyroxin /549/. This difference in the transformations of the triiodinated component in vivo may be partly explained by the fact that it forms rather weak, easily disrupted bonds with the plasma proteins and the tissues. But there is also another opinion, according to which thyroxin is not itself hormonally active and is transformed into an active form only in the tissues. This opinion is held by Gross and Pitt-Rivers /333/. It was tested by Albright, Larson, and Tust /160/, who showed the in vitro deiodination of thyroxin into triiodothyronine by kidney sections.

The possibility of the formation of l-3,5,3' -triiodothyronine in the organism, in tissues other than the thyroid gland, is of great interest, as it is of major importance for solving the problem of the peripheral form of the thyroid hormones acting at the cellular level, a question which has not been clarified Therefore it is not surprising that the study of the transformation of thyroxin into triiodothyronine has been taken up by many leading scholars, but an absolutely definite answer to this question cannot be given yet.

After the reports of Albright and others on the transformation of thyroxin into triiodothyronine by sections of rat kidneys, Sprott and Maclagan /537/ demonstrated the deiodination of thyroxin by tissue homogenates Although they measured only the liberation of free iodine, they assumed that triiodothyronine could be formed [illegible]

[illegible] whose thyroid glands did not function

Analogous observations were made by Gross and Pitt-Rivers even earlier, when they noticed the appearance of an unknown iodionated component in the blood (which [illegible]

[illegible] ronine formation from thyroxin /391/.

But Maclagan and Sprott, showing the deiodination by homogenates of various tissues /408/, reported that the enzymatic system deiodinating thyroxin and triiodothyronine is very resistant to temperature and becomes totally inactive only after two hours of boiling at 100°. It is possible that two different deiodinating systems are involved.

Nakano and Shimizu /437/, studying the transformation of thyroxin in tissue sections, could observe the formation of triiodothyronine only in the kidneys. In other tissues, and even in the liver, it was not possible to observe this transformation

Previous results on the formation of triiodothyronine from thyroxin were very

in the organism After administration of thyroxin the greatest activity was observed in the stomach; a lesser one, although higher than that of the blood,was found in the kidneys and liver Thyroxin was not fixed in the thyroid gland, but after administration of this hormone it was always possible to find a small activity in the brain Activity after administration of labeled thyroxin was mainly found in the composition of the hormone.

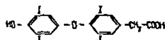
After administration of diiodotyrosine, apart form the thyroid gland and the gastrointestinal tract, a higher activity than that of blood was also found in the kidneys, but radioactivity appeared in the form of iodide.

Experiments with physiological doses of thyroid hormones show a great similarity in the behavior of various tissues in relation to the four thyroid hormones In all tissues, 3,5,3'-triiodothyronine becomes more speedily fixed than 1-thyroxin or 3,3',5'-triiodothyronine 3,3'-diiodothyronine disappears very speedily from the blood Only traces of it remain an hour after injection to healthy persons, as well as to patients suffering from a disturbance of thyroid gland function, the greatest part is excreted in urine in the form of inorganic iodine during the first 24 hours In all cases the liver and,to a lesser extent, the gastrointestinal tract and the kidneys are organs in which the main localization of radioactivity takes place For example, in rats receiving 5 μg of 3,5,3'-triiodothyronine or 1-thyroxin one hour after injection 16% of the triiodinated hormone and 12% of the thyroxin are found in the liver, respectively 3 2 and 1 2% in the kidneys, and 1.1 and 2 1% in the plasma This distribution of the thyroid hormones in the organism underlines the especially important role of the liver in their metabolism In all cases the liver has the leading role in the excretion of hormonal iodine and 16 days after administration of labeled thyroxin it contains about 50% of the remaining activity The problems of the intrahepatic metabolism and of the role of biliary excretion will be examined later

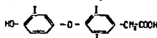
The thyroid gland does not fix the injected hormones and they are very possibly equally distributed in all the tissues, except the liver and the gastrointestinal tract

Hormonal iodine inside the cells forms cellular iodine bound to the protein Extensive studies on the PBI of tissues were performed by Carr and Riggs /236/ on dogs These studies showed that the quantity of PBI is smaller in the skeletal muscles than in the plasma and considerably higher in the liver and kidneys, in other tissues PBI is found approximately on the same level as in the plasma Carr and Riggs further note that the quantity of PBI bound in the tissues and the metabolic activity of the hormones are not in full accord, thus, for example, sections of brain, spleen,and testes of thyroidectomized or hyperthyroid rats did not show differences in oxygen consumption compared to other tissues, although they contain a considerable quantity of PBI. There is no PBI in erythrocytes/473/ and PBI is not found in considerable quantities in cerebrospinal fluid, which is explained rather by the low protein content than by barrier hindrances

The anatomic localization of the hormone in the cells has not yet been determined. The study of the PBI distribution in the structural elements of the cells in liver homogenates of rats from which the thyroid gland had been removed three days after administration of labeled thyroxin could not show any perceptible [illegible]



3355'- tetraiodothyroacetic acid



335'- triiodothyroacetic acid

tetraiodo-and triiodothyroacetic acid, and triiodothyronine into triiodothyroacetic acid. The enzymes participating in this process may be transferred from the mitochondria into the solution. During the last 2-3 years, further confirmation of the excretion of acetic acid derivatives in bile and urine has been obtained The formation of acetic and propionic acid derivatives during the transformation of thyroxin and triiodoohyronine, labeled by I^{131} in positions 3', 5' and 3' respectively, in sections and homogenates of the brain of chicks,was shown in the work of Tata,Rall,and Rawson /563/. Although they did not succeed in definitively identifying the products formed, their studies confirm the existence of deamination processes of the thyroid hormones in the tissues. One of the thyroacetic acids was discovered by Roche and others /485/ in the kidneys of rats and in muscle, after administration of 3, 5, 3' - triiodothyronine.

On the basis of the above results, it is appropriate to ask the following question· to what degree are iodothyroacetic acids products of the metabolism of iodothyronines and to what degree can they ensure the hormonal activity of iodothyronines? If this were so, degradation by way of decarboxylation of the corresponding thyropyruvic acids whose presence in the urine and bile is proved /496/ could be the main pathway of iodothyronine metabolism.

In view of the fact that the tetra- and triiodothyroacetic acids are persistently considered by some authors to be normal products of the intracellular metabolism of thyroid hormones, a considerable number of works have been published on the metabolism of these components, after the administration of I^{131}-labeled acetic acid derivatives of thyronine. Studies made by Larson and Albright /389/, as well as by Roche and others /485/ on humans with the intention of comparing the metabolism of 3,5,3' -triiodothyroacetic acid with that of 3,5,3'-triiodothyronine and thyroxin showed that the acetic acid derivative does not accumulate in such organs as the heart, kidneys,and skeletal muscles and is speedily excreted from the organism, particularly through the intestine.

According to the above-mentioned experimental results mainly obtained by the group of Roche and Michel, the latter authors proposed the hypothesis of two metabolic pathways for the thyroid hormones in the tissues /484/. The first pathway, due to the metabolic activity, leads through oxidative deamination of iodothyronines to the formation of iodothyropyruvic homologues and, through decarboxylation of the latter, to the iodothyroacetic acids. This is the basic metabolic pathway of thyroxin and triiodothyronine, ensuring the formation of active forms of thyroid hormones.

The second pathway, which is general for all tissues,although relatively less important, includes only the degradation of hormone surpluses entering the receptors.

recently examined by Lassiter and Stanbury /393/ on six patients who did not exhibit *absorption of radioactive iodine by the thyroid gland*, after administration of chromatographically pure labeled thyroxin in a dose of 20 to 100 μ g. Using descending paperchromatography in a system of solvents ensuring maximum separation of thyroxin from triiodothyronine, the authors could not confirm previous works from the same laboratory, which showed that triiodothyronine appears in the blood as *a result of extrathyroidal thyroxin degradation. The authors nevertheless do not* reject the possibility of such a degradation in general and emphasize that their results only point to the fact that triiodothyronine, which normally exists in the plasma, is not a deiodination product of the circulating thyroxin.

The research of Lassiter and Stanbury established that the system used for *chromatographic* separation of the iodinated amino acids — butanol-dioxane-ammonia- was very unsatisfactory for the differentiation between close spots of thyroxin and triiodothyronine. It is possible that previous results obtained by Pitt-Rivers and others were the consequence of artifacts arising from the relatively unreliable system of solvents. It seems that such a report permits us to decide definitively that the only source *synthesizing the triiodothyronine circulating in the blood is in the thyroid* gland. The group of Roche and Michel had criticized from the very beginning the possibility of the formation of any large quantities of triiodothyronine by way of deiodination of thyroxin.

At the same time, the formation of 3,3' -diiothyronine in the tissues during *deiodination of hormones richer in iodine has been proved for a number of tissues.* Thus, Tata /561/, Roche, Michel,and others /495/ showed the presence of 3,3'-diiodothyronine in the muscles and kidneys of thyroidectomized rats, after the administration of I^{131}-triiodothyronine.

The discovery of a less iodinated derivative in the tissues, after injection of *tetra-and triiodinated components, raises the question of the deiodination process* as a normal metabolic pathway of the thyroid hormones The normal process of metabolism of the thyroid hormones in the tissues should lead to the formation of an active form of the hormone at the cellular level, having the capacity of acting [illegible]

are considered today from the aspect of the formation of such active compounds.

From this point of view the question of deiodination as being a necessary step in the metabolic transformations of thyroxin in the tissues does not find any confirmation. If triiodothyronine is considered as being the active form of the thyroid hormones, it should exhibit its effect without any latent period, or should at least act faster than the tetraiodinated analogue. But,in fact, the latent periods of triiodothyronine and thyroxin were found to be identical. Together with this a thyroxin antagonist, n-butyl-4-hydroxy-3,5-diiodobenzoate,was found /410, 610/ which did not exhibit such properties in relation to triiodothyronine. It is possible to deduct from this, *as was noted by E.A. Kolli /82/, that this benzoic acid derivative inhibits the trans*formation of thyroxin into triiodothyronine, possibly by way of inactivating a certain enzymatic system which deiodinates thyroxin.

But, recently, more and more results accumulated on the possibility of another metabolic pathway for thyroxin and triiodothyronine, a process during which the thyronine ring remains intact, but where a change takes place in the alanine chain. 3,5,3'-triiodo- and 3,5,3',5' - tetraiodothyroacetic acids, synthesized by Pitt-Rivers, had an immediate action on respiratory metabolism /574/. This led to the question of the formation of oxyacetic derivatives of thyroxin and triiodothyronine in the tissues, in the process of the metabolism of the hormonal precursors.

In a recent work Tomita, Lardy, Larson and Albright /582/ showed that kidney homogenates of rats and mitochondria transform thyroxin into

numerous studies. Albert and Keating /179/, Myant and Pochin (cit. from Berson, /214/) found that thyroxin administered to the blood is speedily absorbed by the liver; 36 hours after administration of labeled thyroxin, there is more hormone in the liver than in the whole organism. This served as a basis for the study of the metabolism of the thyroid hormones in the liver. The perfusion of the liver by a fluid containing thyroglobulin leads to its degradation, with the liberation of iodide. Bile contains these salts after administration of the hormone; the liver effects their physiological destruction, but it is difficult to assume that the metabolism of the hormones in the liver is the same as in other organs, for the function of the liver in regard to detoxication of surpluses of iodothyronines may be a special form of metabolism of the thyroid hormones.

This function of the liver was studied in dogs after the administration of I^{131}-labeled thyroxin and triiodothyronine to intact and hepatectomized animals /302/. In the control dogs all the iodine of the blood and urine was found in the form of I^{131}-thyroxin, triiodothyronine, or iodide. In hepatectomized dogs the hormones progressively disappeared from the blood, but slower than in the control animals, the quantity of iodides was small. Glucuronides of thyroxin or triiodothyronine and also tetra- or triiodothyroacetic acids were found in the blood and urine. A considerable part of the radioactivity was found in a compound of unknown nature.

On the basis of the existing published results it is possible to accept a double role of the liver in the metabolism of the thyroid hormones: on the one hand, the liver effects the degradation of surpluses of plasma hormones, on the other hand, it regulates the quantity of blood hormones, by means of the intrahepatic circulation of their derivatives

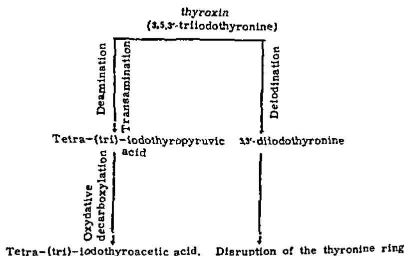
The dissociation of the hormones of the thyroid gland in the liver is related to processes of deiodination, after which further degradation of the structure of thyronine takes place and in this manner the hormone completely leaves the metabolism. The liver also excretes into the bile free thyroxin in the presence of considerable surpluses and in this manner eliminates toxic quantities of thyroid hormones. Apart from this, the liver forms paired compounds of free hormones with glucuronic acid and, to a small degree, with sulfuric acid, thus blocking active hormonal compounds. This process is also directed to their excretion, for glucuronic compounds of iodothyronines are not found in the blood stream, except in cases of occlusion of the bile ducts.

The processes of intrahepatic transformation of the thyroid hormones could be studied in detail upon administration of physiological doses of various iodinated thyronines, with labeled I^{131} in the thyronine ring, or C^{14} in the carboxyl The hepatic metabolism of l-thyroxin, l- 3,5,3' -triiodothyronine and l-3, 3'-diiodothyronine was studied by many researchers. The most important discoveries were made by the groups of Chaikoff, Beraud, and Vannotti /213/, Myant /433,434/, and especially by the school of Roche and Michel /495,499/. As was determined by these authors, administration of labeled thyroxin and di- or triiodothyronines to thyroidectomized rats was accompanied by the excretion of a mixture of radioactive products in bile. Among the components formed it was possible to find, apart from iodides and the free hormone, a series of particular substances characteristic of the hormone administered. The most important of these components were determined. It should be noted that derivatives of 3,5,3'- triiodothyronine were not even found in small quantities in the bile after administration of thyroxin. This constitutes indirect but important evidence against the formation of triiodothyronine in the liver, as a result of thyroxin deiodination

The high radioactivity found in the liver of a rabbit or a rat having received one of the isomers of thyroxin is only provoked to a very small extent by radioactive iodine. A similar high radioactivity is found after administration of l- 3,5,3' -triiodothyronine or its geometrical isomer, or of 3,3' -diiodothyronine

It includes deiodination of tetra- and triiodothyronines into 3,3-diiodothyronine, which is a preliminary condition for the disruption of the oxygen atom, binding the benzene rings in the structure of thyronine. This reaction is effected by oxidases. This hypothesis looks quite harmonious and is based on a series of factors obtained during the study of cellular degradation of iodothyronines. But all these facts are only an indirect support of the above hypothesis; its definite proof evidently demands further study, with quantitative evaluation of the metabolism in both directions, and also more convincing proofs of the hormonal role of the triiodothyroacetic derivatives at the cellular level. During the last two years, it seems to us, there have been no significant experimental confirmations, if we disregard a series of studies touching the immediate action of triiodothyroacetic derivatives on the respiration of tissue sections. This question shall be dealt with in detail later.

Thus, although there still is a number of unclarified aspects of the intracellular degradation and the active form of the thyroid hormones, the general pathway of their metabolism in the organism may be shown in the following manner:



4. The Metabolism of the Thyroid Hormones in the Liver

The liver is, to a certain extent, a target organ for the action of the thyroid hormones. On the other hand, the liver has an extremely important role in regulating the thyroxin circulating in the blood and in the detoxication of its surplus quantities. The liver is, for the moment, the only organ in which it is possible to observe the processes of thyroid hormone degradation, while leaving it intact.

In order to clarify the importance of the liver in the metabolism of the thyroid hormones, a considerable number of studies has been made on hepatectomized animals. Large doses of thyroxin in thyroidectomized rats had a stronger action on the pulse frequency if subtotal hepatectomy had been previously performed on these animals /179/. Small doses of thyroxin, corresponding to about the normal endogenous level, had the same effect on hepatectomized as on nonhepatectomized rats. These facts show that the liver speedily renders inactive surplus quantities of thyroxin, and thus stops the augmentation of the hormone quantity in the blood.

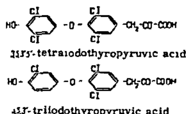
It has been known since 1919 that the liver fixes circulating dl-thyroxin, and that this substance may also be found in bile. This fact was later confirmed by

Free iodothyronines are found in feces, but always in much smaller quantities than in the bile of animals having a fistula, to whom identical quantities of the hormones were administered. These results permit us to assume that a consider- [illegible]

ensure a very precise regulation of the quantity of iodothyronines in the blood.

Apart from excreting thyroxin in a free state or in the form of a glucuronide, the liver also disposes of the oxidizing enzymes, which, in various ways (decarboxylation, deamination) degrade thyroxin. After a subcutaneous injection of C^{14} OOH-labeled thyroxin rats excreted within 12 hours 31% of the C^{14} of which 20% were in the bile, 10% in exhaled CO_2, and only one percent in the urine (probably in the CO group of urea, /383/).

After injection of tetra- and triiodothyronine homologues, they were also found in the form of 3,5,3'-triiodothyropyruvic acid and 3,5,3',5'-tetraiodothyropyruvic acid:



3,3',5'-tetraiodothyropyruvic acid

3,5,3'-triiodothyropyruvic acid

The corresponding derivatives are probably formed from other derivates of thyronine. The 3,5,3-triiodinated product was found in abundant quantities in the bile of thyroidectomized rats, which received 2μg of its hormonal precursor. 3,5,3'5' -tetraiodothyropyruvic acid was at the first found in urine and later identified in the bile of rats subjected to the action of l- thyroxin.

The hepatic metabolism of iodothyronines in relation to the processes of oxidative deamination is in all probability similar to the metabolism of the compounds of the same type. This reaction may be based on the direct action of l-amino-oxidase, or on the participation of transamination, as it occurs during the metabolism of tyrosine /21/, or during the formation of 3,5-diiodo-4- hydroxyphenylpyruvic acid from diiodotyrosine in liver sections. Evidently, the deamination process is not a general mode of hormone degradation and it takes place in the liver to a considerable extent, as iodothyropyruvic acid is found simultaneously in the liver, bile, and urine after administration of the corresponding precursors. As even a trace of iodothyropyruvic acid is not found in the blood of rats with ligated bile ducts, while hormones of hepatic origin bound to glucuronic acid may be found, it seems probable that the kidneys metabolize the hormones to the same extent as the liver, and that the derivatives that they excrete are results of their own metabolism.

The discovery of thyropyruvic acids in the liver and urine attracts our attention

The remaining iodinated compounds found in the bile after administration of labeled iodothyronines could be identified by chromatographic separation on paper or on columns. Upon chromatography glucuronic derivatives of the phenol components of the hormone are found in all cases. These conjugates, *separated by elution from* the chromatogram, form iodothyronines by processing with β - glucuronidase of the spleen and of E. coli. The removal of the compounds separated from the chromatograms is not effected by peptidases but by glucuronidase, which is also proof of the fact that the phenol group of thyroxin is bound to glucuronic acid. This conclusion is also confirmed by the fact that, upon administration of thyroxin labeled by C^{14} in the COOH group,all the activity in the bile is liberated in the form of CO_2, after developing with ninhydrin. In view of the fact that ninhydrin only removes CO_2 from amino acids when both the carboxyl and amino groups are free, it is possible to conclude that the thyroxin excreted in bile is not bound in the form of a peptide /383/. Experiments in which organic iodide I^{131} was injected showed that endogenous thyroxin, forming from the administered iodide, also appears in the bile in the form of glucuronides. Other proofs have been brought, confirming that these conjugates are precisely glucuronic compounds of iodothyronines. Similar compounds also were formed in liver sections, but not in homogenates, sections of the liver exhibited small activity, and sections of the heart, the diaphram, the spleen, and the brain were not capable at all of forming glucuronic conjugates of thyroxin.

Thus, various iodine containing parts are found in the bile of animals receiving thyroid hormones, glucuronic and sulfuric ethers of the thyroid hormones are also found in urine. Thus for example, after administration of labeled triiodothyronine to dogs with an occlusion of the bile ducts, Flock, Bollman, and Grindlay /301/ found an augmented excretion of radioactivity in the urine, while they determined the presence of radioactive compounds in it, including iodine and the glucuronic conjugate of triiodothyronine Further studies show the appearance of disulfate compounds *of triiodothyronines* /481,489/.

The capacity of the liver to bind thyroxin in the form of glucuronic compounds is nevertheless limited. After administration of large doses of I^{131}-labeled thyroxin, its main quantity is excreted with the bile in the form of unchanged thyroxin. The administered thyroxin first appears after injection in a bound state and later in a free state in the liver. Reabsorption of the thyroxin excreted into the bile is slight.

In his works Myant /433,434/ gave the results of studies made with I^{131} - thyroxin on the excretion of the hormone in the bile and in the intestine of healthy people. According to his results glucuronic derivatives appear in the bile after the administration of radioactive thyroxin, they enter into the intestine and are mostly lost with feces. Reabsorption from the intestine constitutes only 30% of the thyroxin excreted in the bile.

Gross and Leblond /329/ found that 24 hours after intravenous injection of 800 μ g of I^{131}-labeled thyroxin to rats 70% of the administered activity are found in the feces. After administration of 1,300 μ g of thyroxin, 85% of the I^{131} contained in it *were excreted in feces within 6 days.* Whereas a part of the hormones returns to the blood stream after the hydrolysis of their glucuronic compounds, their degradation excludes them definitely from the metabolic cycle. Upon administering a physiological dose of one μ g to a rat weighing 200 g, up to 70% of the administered 3,5,3' [illegible]

The importance of the salivary glands in the metabolism of iodine was at one time emphasized. A number of authors /290, 601/ thought that the salivary glands play an important role in the deiodination of the intermediate metabolic products of the thyroid hormones and participate in regulating the absorption of iodine by the thyroid gland. But this opinion did not find any confirmation in later research and it was shown that the removal of the salivary glands does not change the distribution, the rate of disruption, and the excretion of the exogenous thyroid hormone /432/.

Ruegamer /510/ studied the role of the salivary glands in the metabolism of iodine in the process of deiodination, by administering to rats and dogs with and without salivary glands diiodotyrosine, thyroxin, triiodothyronine, and iodide. He came to the conclusion that the salivary glands do not participate in the metabolism of diiodotyrosine and in the regulation of its level in the blood.

Thus, at the present time, most authors do not credit the salivary glands with any special role in the metabolism of iodine in the organism, although some of them still suppose that they participate in the process of deiodination, and even in the formation of mono- and diiodotyrosines, which, according to their opinion, later follow the blood stream, enter the thyroid gland, and serve for the production of thyroid hormones.

It is absolutely necessary to say a few words about the metabolism of the thyroid hormones in the brain and the pituitary, especially in view of the fact that there exist close interrelations between the action of the thyroid gland and that of the pituitary and of the thyroid hormones on the central nervous system. The metabolism of the thyroid hormones in the pituitary and in the brain was studied by way of administering labeled hormonal preparations to animals in vivo, as well as by adding labeled hormones to preparations of brain tissue in vitro.

Sturm and Wernitz /554/, administering radioactive iodine subcutaneously to rats and guinea pigs, made after 2 hours an autoradiographic study of the iodine distribution in the anterior and posterior lobes of the pituitary, in the tuber cinereum, in the hypothalamus, in the lobes of the brain, in the cortex of the brain, and in the cerebellum. No particularities were observed by them as to the distribution of iodine. These regions of the brain contained considerably less iodine than the liver. At the second stage of the study, 24 and 48 hours after the injection, a considerable accumulation of iodine was noted in the anterior and posterior lobes of the pituitary, in the hypothalamus, and in the tuber cinereum. Even the frontal lobe was, surprisingly, found to contain considerable activity. During their study the authors did not determine the iodine fraction, but they showed that the iodine accumulated after 24, 48 hours is hormonal iodine. This led the authors to conclude that the incretion elaborated peripherally has an affinity for certain regions of the brain, while the diencephalon and the cortex occupy a particular position in this respect.

Wide research on the metabolism of the thyroid gland hormones in the pituitary and in the brain were made by Ford and Gross /306/ by administering I^{131}-labeled thyroxin and triiodothyronine to rabbits After intravenous injection of relatively small doses of the labeled hormone activity was observed to accumulate to various extents in the different parts of the brain and of the pituitary.

As has been shown in previous research, the iodine itself is not concentrated in the pituitary or the brain, neither after 2 hours /252/, nor after 4 hours /368/. Radioactivity is later found, but its total disappearance was noted after thyroidectomy. Analogous results were obtained for rats and guinea pigs. Sloviter and Morel /533/ recently threw light upon the further study of the metabolic process, showing that upon administration of radioiodine to rabbits kept on a diet with low iodine content it accumulates after 48 hours in the anterior and posterior lobes of the pituitary, a considerably higher activity was observed during this time in the posterior lobe.

from another point of view: their oxidative decarboxylation may lead to the formation of acetic acid derivatives of thyronine, which, according to the results of Thibault et al. /574/, have an immediate effect on the rate of metabolism, without a latent period. Thyropyruvic acids may really be the precursurs of thyroacetic acids and, if this is so, the formation of thyropyruvic derivatives in the cells should be the first stage in the metabolism of iodothyronines

If the metabolism of the thyroid hormones in the liver is considered as a definite transformation, in view of their action on the metabolism in the liver (as in other tissues), then the participation of the liver in the metabolism of iodothyronines is expressed by two processes of extreme importance in the regulating mechanism of the level of circulating active compounds. In the final analysis the role of the liver in the metabolism of the thyroid hormones is that it concentrates plasmatic surpluses in order to destroy one part of them and to include the other into the mechanism regulating the hormonal level of the blood by a mechanism based on the intrahepatic circulation.

The kidneys also play an important role in the metabolism of thyroid hormones. After administration of various labeled iodinated amino acids to the organism, the greatest activity is observed in the liver and kidneys. It has been noted already that, if the transformation of thyroxin into 3,5,3' -triiodothyronine occurs in the organism, this process takes place in the kidneys only. The kidneys, like the liver, actively degrade the thyroid hormones into deiodinated thyropyruvic and acetic acid derivatives, which are later excreted in urine in the form of glucuronic conjugates. It has been shown by Roche, Michel, and others /482, 488/ that after the administration of 3, 5, 3'-triiodothyronine to rats, a considerable part of it is excreted in urine, while small quantities of the glucuronide of triiodinated thyronine also appear in the urine. The formation in the kidneys of 3,3'-diiodothyroacetic acid, after administering 3,3'--diiodothyronine labeled in the position 3', was demonstrated by Roche, Michel, Nunez, and Jacquemin /491/ by the radiochromatographic method. The results obtained show that the diiodinated analogue of thyroxin is subjected to deamination in the tissues, with formation of 3,3' -diiodothyropyruvic acid, which, becoming decarboxylated, is transformed into 3,3' -diiodothyroacetic acid.

5. The Metabolism of the Thyroid Hormones in Other Organs

Our knowledge of the metabolism of the thyroid gland hormones in other organs is still insufficient. This is explained on the one hand by the small concentration of hormonal iodine in them which renders their study difficult, even by such sensitive methods as those of labeled atoms and chromatography. On the other hand, studies made up to now have not brought to light anything new on the metabolism of the thyroid hormones in the other organs, compared to their metabolism in the liver or kidneys.

After administration of labeled thyroxin and triiodothyronine, the appearance of inorganic iodine was noted in skeletal muscles, diaphragm, and tissues of several other organs, which points to a process of deiodination occurring in them But the question of the formation of other products of thyroxin and triiodothyronine metabolism in the above organs and tissues is still disputed. Roche and others /493/, after administering I^{131}-labeled triiodothyronine to rats found diiodothyronine as well as 3, 5, 3'-triiodothyroacetic acid in the butanol extract of the skeletal muscles and diaphragm. At the same time, Tata /561/, working with muscle homogenates, determined a speedy degradation of thyroxin and triiodothyronine, but iodide was in

pituitary hormone secretion. It is well known that the hypothalamic centers regulate the activity of the thyroid gland. It is an accepted thought that the concentration of the thyroid gland hormones in the hypothalamus regulates the level of the thyroid hormones in the portal vessels of the pituitary. They may in turn change the hormone contents of the thyroid gland, to which the adenohypophyseal cells are sensitive /229/.

But the results of Ford and Gross do not concur with this hypothesis. It is difficult to suppose that the concentration of triiodothyronine in the hypothalamus may have a considerable influence on the high capacity of the adenohypophysis to concentrate triiodothyronine. It is more likely to assume that the concentration of the thyroid hormones in the hypothalamus is associated with the production or liberation of several neurosecretory agents, which stimulate the secretion of the thyrotropic hormone (TSH). In this relation it may be thought that the hypothalamic concentration of triiodothyronine is a factor with the help of which triiodothyronine acts in a stimulating manner on the production of the adrenocorticotropic hormone (ACTH) /281/. But there are results showing that the injection of thyroxin into the hypothalamus does not have an inhibiting effect on the thyrotropic hormone, while injection of thyroxin into the adenohypophysis really lowers the function of the thyroid gland.

The concentration of the thyroid gland hormones in the neurohypophysis may be related to the influence of this hormone on water metabolism. This assumption is acceptable in view of the fact that the concentration of thyroxin in the posterior lobe of the gland is parallel to the antidiuretic activity of the pituitary This also concurs with the fact of the augmented absorption of thyroxin by the neurohypophysis during hypothyroidism and reduced absorption during hyperthyroidism.

The concentration of triiodothyronine in the grey matter the brain is also of a certain interest. Its distribution there parallels the distribution of radioactive methionine, which was used as an indicator for the intensity of protein synthesis in the brain. It is possible that this shows the extent of the myelinization of the brain under the action of thyroxin. Such concurrence between the concentration of triiodothyronine and the rate of anabolic activity, discovered in other tissues, has a surprising resemblance to its distribution.

The study of the metabolism of the thyroid hormones by means of tissue preparations of rat brains, made by Tata, Rall, and Rawson /563/, show that, in the brain as well as in the liver and kidneys, processes of iodine separation from l-thyroxin and l-3, 5, 3'-triiodotyronine take place, as well as processes of deamination. Tetraiodothyro- and triiodothyropropionic and (or) acetic acids are formed as a result of these transformations. Their identification was found to be impossible, for, even upon using two-dimensional chromatography, they had identical *Rf* values. Studies confirm that this process has an enzymatic character, for the effect disappears upon heating to 100°, although it takes place also in anaerobic conditions and upon adding cyanides. The deiodination process is proved by the discovery of iodine ions. According to the results of these authors, they succeeded in finding, upon incubating thyroxin, the appearance in some cases of small quantities of triiodothyronine.

All that has been said shows that the intracellular metabolism of the thyroid gland hormones has general traits for a number of tissues of the organism, which are expressed in the processes of deiodination and deamination. Together with this, there are some particularities in the metabolism of the thyroid hormones in the liver, kidneys, brain, and pituitary. It may be considered as proved that thyroxin and the triiodinated analogues transform into acetic acid derivatives, which later appear in the bile, urine, and feces in the form of glucuronic conjugates. Processes of deiodination undoubtedly also take place. Experimental research, made up to this

Thus, the ratio of activity $\frac{\text{organ}}{\text{plasma}}$ for the anterior lobe was 0.8 (from 0.5 to 1.4), and for the posterior lobe 3.2 (from 1.3 to 6.2). This led to the conclusion that the thyroid hormone accumulates in the posterior lobe of the pituitary and is there deiodinated.

It may be accepted that the same picture that is observed in relation to endogenously formed hormone is obtained after injection of radioactive thyroxin. Courrier and others /252/ obtained a ratio of 0.4 and 3.2 for the anterior and posterior lobes of the pituitary 120 minutes after administering about 1.3μg of labeled thyroxin/kg.

Differences in the rate of the concentration reduction after administration of exogenous thyroxin and after inclusion of endogenous hormones give the basis to the affirmation that part of the endogenous hormone in the plasma is found in the form of triiodothyronine. This is more probable, notwithstanding the fact that the main mass of organically bound iodine in the pituitary exists in the form of thyroxin in the metabolic process of the endogenous hormone.

Autoradiograms, made by Jensen and Clark /368/, showed that after administration of radioactive thyroxin the activity in the adenohypophysis is also distributed in a diffuse manner on the parenchyma of the whole gland. The level of thyroxin concentration is, generally speaking, proportional to the level of thyroxin in the plasma. It may be thought that, notwithstanding the relatively small quantity of thyroxin in this organ, it is important from the biological point of view, for the interrelationship between the production of the thyrotropic hormone and the level of thyroxin in the blood stream are well known.

Triiodothyronine concentrates in the brain as well as in the pituitary; in the latter it is found in both lobes. The possibility of its formation from thyroxin in the anterior lobe of the pituitary is based on observations of Slovitег and Morel /533/. But, it is more probable that the source of triiodothyronine in the pituitary is the triiodinated hormone of the blood stream, although this has not been proved chromatographically.

The presence of iodine in both lobes of the gland after administration of radioactive hormones may point to processes of deiodination. It was found by chromatographic separation, with the use of two-dimensional chromatography employing as [illegible]

and adding labeled hormone.

In contrast to the results obtained by Tata and others, [illegible]

Upon comparing the distribution of equal doses of thyroxin and triiodothyronine, an almost identical ratio between the concentrations of triiodothyronines and thyroxin was found to prevail in almost all the tissues studied. According to the iodine content it is equal to 2.5 and according to the concentration of iodothyronines to 3. These relations are of the same order as the comparative biological activity of the two components and may possibly reflect a quantitative difference in their action.

From the aspect of the biological importance of the localization of these hormones the concentration of triiodothyronines in the pituitary, in the paraventricular nuclei, maybe related to the mechanism of hypothalamic-pituitary regulation of the

Chapter V

THE ACTION OF THE THYROID GLAND HORMONES

(Deistvie gormonov shchitovidnoi zhelezy)

The thyroid gland has a very strong influence on the vital activity of the whole organism Upon elimination of the function of the gland serious disorders begin in the chemical and morphological structures, which are manifested in the form of various somatic and psychic defects

The manifold action of the thyroid gland hormones on physiological functions, on the rate of the metabolic processes, on the activity of various enzymatic systems, on the organism as a whole, as well as on tissue preparations, has already been known for a long time. Our knowledge on the role of the thyroid gland hormones is based on experiments with the administration of thyroid hormone to healthy and athyroid animals, on wide clinical observations on patients with hyper- and hypothyroidal states.

The influence of the thyroid hormones on the organism is expressed in the *form of a reaction by whole systems of organs as well as by separate physiological* functions and morphological structures. The influence of the thyroid gland secretions leads to changes in growth and metamorphosis, in oxygen consumption by the whole organism or by tissue preparations in vitro, and in various aspects of the metabolism and activity of various enzymatic systems. The great variety of the effects observed after administration of the thyroid hormone may reflect the initial action of this hormonal substance on one link which lies at the base of the biochemical processes in the cell, or on one morphological structure which is responsible for the correct integration of the processes at the cellular level These questions shall be later examined in detail. It should be noted here that, when we speak of the action of the thyroid hormone, this term is not only used in relation to compounds produced in the thyroid gland, but has a group significance, implying any substance having a favorable effect upon administration in a proper manner to a patient suffering from myxedema Consequently, such a definition does not demand that the substance be attributed to a given group, or fulfill any special requirement as to its origin or structure. Numerous studies have shown, however, that all the compounds possessing the biological activity of the thyroid hormones are related to the chemical group of thyronine, in whose aromatic rings atoms of iodine are contained.

At the present time, we know of various forms of thyroid gland hormones, including thyroglobulin, various products of its degradation, thyroxin from thyroglobulin (or synthetically obtained), other substituted thyronines, various crystalline products from hydrolysates of iodinated protein, and circulating forms of the thyroid hormones All these substances possess greater or lesser physiological activity, but it is a certain fact that the thyroid hormones produced in the thyroid gland have the strongest biological effect per mole.

Upon examining the question of the action of the thyroid gland hormones in the

time, does not permit definite determination of the importance of each of these processes in the metabolism of hormonal iodine, nor a solution of the question of the general metabolic pathways and specific transformations in various organs. It is difficult to state that in all organs except the liver, kidneys, brain, and pituitary degradation has no important physiological role in the process of regulating the rate of the cellular metabolism of the thyroid hormones. These questions demand further research. But the importance of clarifying the intermediate and the end products of the thyroid hormone metabolism in the tissues should not be slighted, for it is possible that in this way it will be possible to discover the hormone actually acting at the cellular level.

Studies made during the last years by V. G. Baranov, E. N. Speranskaya, and D. S. Tendler /16/, also show clearly the action of the thyroid hormones on the higher nervous activity. The processes of stimulation and inhibition of the cortex of the brain are weakened under the action of small doses of thyroidine, having no influence on the oxygen consumption.

R. P. Ol'nyanskaya /108/ made an important contribution to the study of the role of the thyroid gland in the reflex regulation of the metabolism of the higher nervous system. It was shown by studies made in her laboratory that the thyroid gland is the only transmitting link of the cortical impulses which augment metabolism. Experiments in which the thyroid gland of rabbits was blocked by antithyroidal substances showed the considerable participation of the thyroid gland in unconditioned-reflex changes of gaseous metabolism in relation to changes of external temperature. It was shown in the same laboratory that, upon blocking hormone formation in the thyroid gland by administration of methylthiouracil, the reflectory phase of the augmentation of gaseous metabolism after taking food is inhibited. These experiments, made on dogs, prove the participation of the thyroid gland in the realization of the specific dynamic effect of food, in the reflex regulation of the metabolic processes related to feeding. This is also shown by the studies of N. A. Isichenko /63/, who succeeded in revealing the influence of the changes of the functional state of the brain cortex on the rise of blood pressure under the action of thyroidine. All these experimental results, as well as numerous clinical observations, proved beyond doubt the participation of the thyroid gland in the cortical regulation of the activity of the internal organs. It follows that the influence of the thyroid hormone on the central nervous system plays a considerable role in the mechanism of its action on the various physiological functions in the organism as a whole.

Yu Rosner /118/, studying the mechanism of the action of thyroxin in dogs and cats, by stimulating the receptors of the vessels of an isolated intestine loop, observed the direct action of thyroxin on the functional state of the receptors and on the central part of the reflex arch in acute and chronic experiments. If, after preliminary creation of a background of reflectory responses to acetylcholine and potassium chloride, thyroxin is added to the perfusion fluid which passes through the vessels of an isolated intestine loop, a sharp rise of the stimulation of the reflex is observed, which is expressed by the augmentation of the reflex responses to repeated administration of acetylcholine and potassium chloride During this, the author notes the effect on the nervous system after administration of thyroxin after a very short latent period. As to the mechanism of the thyroxin action on the nervous system, according to the author's opinion, changes of the receptors as well as reconstruction of the nervous centers with participation of receptive systems take place in this case.

A report by Benetato and co-authors /19/, very recently published, brings convincing enough support for the opinion on the action of thyroxin on the central nervous system. It was shown by experiments on dogs, whose circulation of blood between head and body was isolated for several hours while maintaining the cerebrospinal tract, that the action of thyroxin administered to the animal donating the blood is first manifested centrally and that from there thyroxin enters the head of the recipient and provokes a rise of metabolism and temperature in the body of the recipient. Peripheral administration of thyroxin during this period (3-6 hrs) did not have any effect. According to the authors' opinion, the encephalic centers have a special sensitivity and exhibit a fast effect, while peripheral influence starts later.

The above results differ considerably from the results found in the scientific literature on the problem of the immediate action of thyroxin on other tissues and on the change of the metabolic indicators.

organism as a whole, we meet two opposed opinions. Some authors adopt the opinion that a nervous mechanism is involved in the action of the thyroid hormones and affirm that the hormone has either a reflex or direct influence on the state of the cells of the central nervous system and effects its peripheral action through them. The other group of scholars holds for the humoral mode of entry of hormones into the tissues of the organism and their direct effect at the cellular level. This question has been examined in detail in a recent survey by S. G. Genes / 40/. There is of course no doubt about the action of the thyroid hormones on the cells of the central nervous system, especially on the region of the diencephalon, including the posterior and anterior lobes of the pituitary This is shown by a series of studies /306/, showing the accumulation of a relatively high concentration of thyroxin and triiodothyronine in the brain after administering hormones labeled with radioactive iodine to the organism. Consequently, the thyroid hormones change the metabolic processes in the nerve tissue and in this manner they act on the central nervous system At the same time, a great number of reports have accumulated in scientific literature on the direct action of thyroxin and other active forms of the hormone on the oxygen consumption of tissue sections and homogenates, on the uncoupling of oxidative phosphorylation by thyroxin acting on the cellular mitochondria, on the effect on enzyme activity, on the metabolic processes of isolated tissues, etc.

Is this the place to doubt the direct peripheral effect of the hormone, apart from the participation of the central nervous system? The action of thyroxin on the nervous elements of the brain is also an expression of its peripheral effect and it is precisely by changing the metabolism of the nerve cells that thyroxin may demonstrate its action through the central nervous system. This is why it seems to us that it is not necessary to regard the two modes of action of the thyroid hormones as opposed the humoral one, with direct action on the tissues and organs, and the nervous one, through the central nervous system. The change of metabolic processes of the cells as a result of the direct effect of thyroxin lies at the root of both. It is logical to accept that the nervous and the humoral modes of action of the thyroid hormones on the peripheral tissues and organs complement each other and that they are both under the general control of the higher nervous system.

1 The Influence of the Thyroid Hormones on the Various Organ Systems

Clinical symptoms observed in patients suffering from hyperthyroidism or hypothyroidal states express the specific influence of the thyroid hormones on some systems of body organs. The influence of the thyroid gland hormones on some organs has recently been studied very thoroughly on sick people as well as on experimental animals.

Influence on the nervous system

The influence of the thyroid hormones on the function of the central nervous system has been, and is still being very thoroughly studied at the present time by Russian scholars. The first works in this direction were begun in the laboratory of I.P. Pavlov In 1924 A.V. Val'
puppies alimentary conditioned
/112/, from the same laboratory,
thyroidine fortifies the stimulation
made by B.M. Zavadovski and his fellow-workers /58/. They determined the influence of small repeated doses of a thyroid gland preparation on conditioned reflexes. Upon giving
ening of the laten
were observed.
and others.

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The above results differ considerably from the results found in the scientific literature on the problem of the immediate action of thyroxin on other tissues and on the change of the metabolic indicators.

Clear-cut changes in the activity of the higher regions of the brain are observed in pathological states of the thyroid gland. Their appearance is accompanied by a series of physiological and biochemical disorders. In myxedema, for example, an increase of the blood circulation rate was observed in the brain. It was shown in a series of studies with tissue sections that the oxygen and glucose uptake by brain tissue is reduced in myxedema.

There are no results on a metabolic change of the thyroid hormones in the brain during hyperthyroidism and thyroidectomy. But, according to the results of G. V. Tutaev and N. A. Isichenko /152/, the iodine content in the brain was sharply lowered after removal of the thyroid gland, especially in the cortex and cerebellum. After hypophysectomy the average iodine content of the brain was 61.7 $\mu g\%$ and in normal people 265.6 $\mu g\%$. It remained low during the first period, as well as a long time after hypophysectomy. A reduction of the iodine content of the pituitary occurred after thyroidectomy, but its relative quantity in the brain rose The authors came to the conclusion that, in the absence of the thyroid gland, the pituitary regulates the distribution of iodine, concentrating it in itself and that, in general, the basic role in the metabolism of iodine in the central nervous system is possibly played not by the thyroid gland, but by the pituitary.

It seems to us that such an affirmation is not supported by the necessary experimental material, showing the character of the iodine-containing components and the quantitative relation between them - facts which it is necessary to know in order to discuss iodine metabolism. Apart from this it is important to determine the following fact where and in what form does the activity first appear upon administering labeled thyroid hormones to the organism? It is known that the function of the pituitary itself, including the absorption of iodine, is controlled by the hypothalamus. As has been mentioned, studies of the iodine distribution in the various regions of the brain by the autoradiographic method, after administration of I^{131}-labeled triiodo-l- thyronine and I^{131}-l-thyroxin, gave a clear picture of the selective localization of hormonal iodine in the bottom of the third ventricle, in the hypothalamic region, and in the pituitary—particularily in its posterior lobe— and this is undoubtedly related to the effect of the hormone on these structures.

Action on the cardiovascular system

The action of the hormones of the thyroid gland on the cardiovascular system is clearly expressed during severe disorders of the heart in the presence of Basedow's disease. It was assumed that the hormones of the thyroid gland have a specific cardiotoxic action, independent of their metabolic effect. Other authors believe that in thyrotoxicosis the heart becomes insensitive to vagal stimulation Besides this, a complementary stress on the heart is created by the speeding up of the metabolic processes in the whole organism, which is observed in hyperthyroidism.

Action on the liver and gastrointestinal tract

The liver is one of the important organs in which the action of thyroxin appears. A [illegible] thyroidism [illegible] of the variou [illegible] and pathomo [illegible] of the liver are often observed in hyper[illegible] sult of infections, poisons, and other factors takes an especially grave course in the simultaneous presence of hyperthyroidism.

According to the results of numerous studies, the administration of the hormones of the thyroid gland considerably increases the rate of the metabolic processes in the liver. The living liver tissue of mice, dogs, rabbits, and guinea pigs, which were fed for a long time with preparations of the thyroid gland, absorbed more oxygen than the tissue of healthy control animals. In people suffering from hyperthyroidism the oxygen consumption of the liver is sharply augmented. The increase in respiration provoked by thyroxin is more perceptible in the tissue of the liver than in other tissues. In the liver tissue of rats which received thyroxin for four days the augmentation of the oxygen consumption was 60% and 40% in kidney tissue, while similar doses of thyroxin led to a relatively insignificant augmentation of the oxygen consumption in the muscles and heart, the brain, ovaries, and spleen did not exhibit any augmentation of oxygen consumption/325/ The contrary is observed upon blocking the thyroid gland by administration of thyrostatic substances, which leads to a deficiency in the organism of thyroid hormones.

According to the results by Milcu /421/, in dogs with a bile fistula, upon obstructing the bile duct, an injection of thyroxin provokes a reduction of the quantity of bile and a reduction of the cholesterol contained in it. According to the author's opinion, this is effected by the inhibition of bile formation in the liver and by a change in the water balance. But there are also contradictory experimental results. The augmented energy metabolism of the liver leads to growth in volume and weight of the liver in experimental hyperthyroidism. Such changes were also observed on a great number of hyperthyroid patients.

During hyperthyroidism, the capacity of the liver to synthesize glycogen from glucose is lowered, the tolerance to glucose is reduced. After feeding with preparations of the thyroid gland the glycogen of the liver is reduced and may disappear completely. The glycogen of the liver is not preserved even after a carbohydrate diet, other hexoses also have no proper effect. The disappearance of glycogen from the liver, provoked by thyroxin, may be stopped by a combined administration of fructose and insulin. The glycogen disappears only from the liver and the cardiac muscle. The glycogen of the striated muscles is not subjected to the influence of the thyroid hormones and changes to a small extent. On the other hand, thyroid insufficiency also leads to a reduction in the glycogen content. It was shown that in thyroidectomized sheep and guinea pigs the glycogen content was only 40–50% of its quantity in normal animals, while the glycogen of the muscles remained unchanged. It may be concluded that normal quantities of thyroid gland hormones are optimal for the maintenance of the liver glycogen level. Loading with galactose in hyperthyroidism often gives abnormal results and this is probably related to the accelerated absorption of galactose from the intestine, peculiar to hyperthyroidism. When choline is simultaneously given thyroxin provokes a reduction of the fats and cholesterol content of the liver /305/

Various functional tests, characterizing the extent and the sequence of disorder of the metabolic processes in the hepatic tissue, are used to determine the functional state of the liver in thyrotoxicosis.

S.F. Mandl' /92/ used in thyrotoxicosis ten different tests simultaneously, examining the protein, carbohydrate, lipoid, pigment, and other metabolisms, reflecting the antitoxic function of the liver. The author concludes that the first to suffer during thyrotoxicosis is the protein metabolism, and then the carbohydrate metabolism becomes disordered and the antitoxic function of the liver is reduced. The lipoid and pigment metabolisms become disordered in the presence of severe forms of thyrotoxicosis.

A.P. Stepanenko /135/, studying the antitoxic function of the liver in various forms of goiter, also notes the severest disorders of the barrier function in the presence of hyperthyroid goiter.

The results of I. A. Drazhevtskaya (*cit. from B. V. Aleshin, /9/*) also show that during thyrotoxicosis the protein synthesizing and detoxicating functions are the first to suffer, while disorders of the lipoid and pigment metabolisms are added during severe forms of the disease.

The disorders of the metabolic processes of the liver influence in their turn the peripheral regulation of the thyroid gland hormones by the liver. M. A. Alekperov /5/ also notes a reduction of the antitoxic synthesizing function of the liver in patients suffering from thyrotoxicosis.

Affection of the liver parenchyma may bring about important changes in the metabolism of the thyroid hormone and augment in some cases the quantity of the hormone in the circulation. This can be explained by the accumulation of the thyroid hormones and their glucuronic compounds in the blood, and by a change in the structure of the protein fractions in the serum, which is related to the affection of the liver. Experimental research made by St. Milcu, L. Vaisler, and E. Kostiner /100/ on dogs suffering from toxic hepatitis provoked by carbon tetrachloride showed a reduction in the capacity of the liver to inactivate thyroxin. The accumulation of radioactive iodine in the liver is also reduced in these animals. The above results point to the role of the liver in the regulation of the hormone content of the thyroid gland and of the plasma and bile iodine.

Action on the endocrine glands

The relation of the thyroid gland to other glands of internal secretion has been known for a long time, but the interrelations between endocrine glands in the regulation of physiological functions, metabolic processes, as well as the possible interactions of the various hormones, are still most insufficiently studied.

We will dwell here only on the action of the thyroid gland on the gonads and the adrenal glands, leaving the examination of its relationship with the other glands of internal secretion to a special section on the regulation of the thyroid gland function.

It is known that a disorder of the whole endocrine apparatus sets in after thyroidectomy the development of the gonads is retarded, atrophy of the thyroid gland sets in, and the anterior lobe of the pituitary and the adrenal cortex grow

There are experimental results showing that athyroid rabbits are capable of developing ovarian follicles, but they have no ovulation. But it is necessary to note that, according to published results, thyroxin does not change the gonadotropic activity of the pituitary. It was shown in experiments that hypothyroidism lowers the sensitivity of mice to estrone and that hyperthyroidism has an inverse effect, while the reaction to estradiol remains unchanged.

The following changes are noted in the adrenal glands. Adrenal hyperplasia was provoked in experimental animals after administration of thyroid hormones. The adrenal glands of those suffering from Basedow's disease were found to be relatively insensitive to the action of ACTH. Prolonged action of thyroxin led to the reduction of the adrenal glands and the rats showed smaller resistance upon exposure to cold. The reduction of the animals' capacity to maintain their temperature also points to a reduction in the production of corticosteroids.

Mikulaj and Nemeth /420/ determined the potential capacity of the adrenal cortex of patients suffering from thyrotoxicosis, by observing the level of 17-hydroxycorticoids after the administration of ACTH. The authors came to the conclusion that

the secretory capacity of the adrenal cortex in patients suffering from thyrotoxicosis is generally adequate during maximum stimulation by ACTH. But during prolonged stimulation with submaximal doses of ACTH this adequate response is replaced by a phase of reduced secretion. Consequently, during thyrotoxicosis, under physiological conditions of submaximal stimulation,the adrenal cortex cannot use its potential reserves in toto. A paper by V. Komissarenko and T. Valueva /84/ has recently appeared, reporting that Hungarian scientists determined qualitative changes of the adrenal cortex secretion during hyperthyroidism and that new substances appeared which are not found in healthy persons. No more detailed developments of these interesting studies have been printed.

The role of the thyroid gland in the reaction of the organism to the action of poisons and toxins

Numerous studies have been made on the action of various poisons and bacteria after thyroidectomy and in hyperthyroidism. Some results show that during thyroidectomy, rabbits and mice are more sensitive to morphine, but other results show that the narcotic effect of morphine does not change in relation to the state of the thyroid gland. Works on the relation of the thyroid gland to morphine are fragmentary and do not give a basis for definite conclusions.

Feeding thyroid gland raises the resistance of rats to the action of several drugs, as for example pentobarbital, thyroidectomy, on the other hand, lowers their resistance. Yet, thyroxin makes animals more sensitive to such preparations as phenobarbital in heavy doses its toxic effect grows upon administering thyroxin.

There is a series of studies on the increased sensitivity of hyperthyroid persons to hormones of the adrenal medulla

Thyroxin probably has an influence on the development and course of a series of infections Thyroid insufficiency predisposes to tuberculosis. This was shown experimentally on animals and was confirmed by clinical observations. It was thus determined, for example, that thiouracil shortens the life span of guinea pigs during tubercular infection. There are reports on the synergistic effect of thyroxin with sulfonamides in the treatment of pneumococcus infections of mice. Thiouracil raises the mortality of mice from poliomyelitis and thyroidine lengthens the incubation period of this disease. Results differ as to the action of thyroxin and cortisone on sensitivity to tuberculosis. Hyperthyroidism limits general fatal infections after internal administration of streptococcus, to local nonfatal inflammations /96/. Consequently, hyperthyroidism strengthens the mesenchymal reaction of the organism against bacterial toxins.

As was shown by the works of A. A. Voitkevich and his co-workers /32, 124/ experimental increase of the concentration of the thyroid gland hormone enhances the augmentation of the general resistance of the organism to various morbid states. They studied the macrophagous system of the organism by its capacity to phagocytize and by other symptoms after thyroidization and methylthiouracil action. Under the action of thyroidine the regeneration of tissues was speeded up, the survival of infected animals was augmented, and the frequency of tumors provoked by carcinogenic substances was reduced, antithyroid substances had an opposite effect. Studies performed by Rumanian scientists under the direction of academician Parchon /452/ showed a favorable effect of the administration of small doses of the thyroid gland hormone during chronic tubercular infection of guinea pigs. According to the authors' opinion, thyroxin has a stimulating effect on the cortex of the brain and leads to the mobilization of the defensive functions of the organism for fighting the infection.

No definite results were obtained by studying the direct influence of the hormones of the thyroid gland on microorganisms. There are reports on the inhibiting as well as the stimulating action of the thyroid hormones on various bacteria.

A relatively large number of works touch upon the importance of the thyroid gland in the anaphylactic reaction. Most results obtained on guinea pigs enable us to affirm that thyroidectomy leads to the loss of the capacity of the organism to be sensitized by a foreign protein. Contradicting results were obtained on other animals (rabbits). It is nevertheless believed that a normally functioning thyroid gland is necessary for the reactivity of the connective tissue, which creates the readiness to anaphylactic and allergic reactions.

The influence of the thyroid hormones on the action of carcinogenic substances in the organism has been shown during the last years. Research in this direction showed that thyroxin lowers the frequency of tumor appearance after the action of benzanthracene and methylcholanthrene, while thiouracil augments the carcinogenic effect. Similar results were also obtained in the works of Voitkevich and his coworkers /32, 48/ . Such an effect is explained undoubtedly by the functional activity of the thyroid gland on the physiological state of the connective tissue. During thyroid insufficiency a rise of receptivity to malignant growths is observed. It was shown by recent studies that many malignant growths of the thyroid gland could have been created as a response of the organism to a demand in thyroid gland hormones, the reaction of a normal gland to such a demand could be the strengthening of its function, as a result of which some undefined changes set in, concerning not only the function but also the morphology of the gland. This may also be explained by a disorder in the synthesis of RNA, provoked by thiouracil as well as by the antimetabolites of uracil. The development of cancer was observed in rats and mice after prolonged action of thiouracil. Thus, in rats receiving allyl thiourea and 2-acetylaminofluorene malignant tumors developed /220, 221/. In mice propylthiouracil provoked the development of cancer. The development of benign tumors under the action of thiouracil was discovered in other works.

The above studies show that prolonged stimulation of the growth of the thyroid gland, possibly through the mediation of the pituitary, leads to the development of tumors of the thyroid gland. The malignant or benign nature of the growth depends on the genetic background and on the exposure to the carcinogen.

2. *The Influence of the Thyroid Gland on Growth and Metamorphosis*

Inhibition of growth and development of the organism sets in upon removing the thyroid gland from experimental animals and in hypothyroidism of people.

[illegible] and this [illegible] is a very sensitive test and is widely used as a method for determining the activity of the thyroid horm [illegible] e metamorphosis, [illegible] thyroxin in this [illegible] similar action.

The clinical manifestations of the arrest of growth and development differ in young and adult animals. In young ones arrest of growth and development leads to dwarfism and to disorders of the higher nervous activity The slowing down of the sexual maturity of the organism *is an invariable symptom of the elimination of the thyroid* function. These changes were confirmed in experiments by many authors, by way of thyroidectomy as well as by blocking the thyroid gland or destroying it with radioactive iodine /69, 71/. In an athyroid state, brought about by the above methods,

considerable changes of the external aspect of the experimental animal set in, besides a sharp underdevelopment of the whole body. The growth arrest of the animals after thyroidectomy probably develops as a consequence of a disorder in the interrelationship between the pituitary and the thyroid gland, for the growth hormone of the pituitary has no effect on these animals. The effect of the thyroid gland on growth is also shown in nonmetamorphosing animals

Thus, normal growth is impossible without a thyroid gland. In adult animals, after removal of the thyroid gland, the main symptoms of athyroidism are the change of metabolism and progressing emaciation. Although these animals exhibit less symptoms of myxedema, a mucous infiltration of the skin may nevertheless be observed in them too. It was earlier thought that thyroidectomy does not have any perceptible effect on adult monkeys, but recent studies making use of thyroidectomy and I^{131} showed that myxedema very similar to that of man appears in monkeys. Undoubtedly the action of the thyroid hormone on growth is a sum of its effects on a large number of biochemical processes, the acceleration of which is necessary for the augmentation of the size of the organism.

Overdosing by thyroxin leads to a considerable loss of weight and to the death of most animals The growth of cartilage, which was studied by the inclusion of S^{35}, is at least partly controlled by hormones of the thyroid gland, being accelerated under the action of thyroxin and slowed down by blocking the function of the gland with thiouracil /280/ Teething is noticeably accelerated by the action of thyroxin. In thyroidectomized rats thyroxin considerably speeds up skeletal maturation Hypophysectomized animals need the growth hormone as well as thyroxin for optimum growth of the skeleton In tadpoles thyroxin stimulates the ossification of the long bones

3 The Action of the Thyroid Gland on Metabolism

Influence on the oxygen consumption

A clear expression of the action of the thyroid gland on various aspects of metabolism is given by its effect on the rate of the metabolic processes, which is expressed by an increase in the oxygen consumption

The surprising action of the thyroid hormones on the oxygen consumption, on the gaseous metabolism, and on the oxidative processes in the organism was noted already many years ago and thoroughly studied on humans as well as on various animals, the studies were made on the whole organism, on living organs, and on tissue preparations Experimental research made by M. M. Pavlov /109/ showed that the elimination of the thyroid function leads to a sharp reduction of the gaseous metabolism The study of the basal metabolism as a criterion of the functional state of the thyroid gland is a generally accepted test and up to this day it was the only possible method of making this examination The action of the thyroid hormone was quantitatively evaluated in healthy persons and in patients suffering from hyper- and hypothyroidism on the basis of the determination of the basal metabolism

In all experiments considerable reduction of exhaled carbon dioxide as well as of inhaled oxygen takes place in absolute and relative quantities after the removal of the thyroid gland

One of the important effects of the thyroid hormones on the organism as a whole is their action on calorigenesis After thyroidectomy there is a reduction of calorigenesis, the body temperature drops, on the contrary, a considerable rise of temperature occurs after administration of thyroid hormones During

suppression of the oxidative processes in the organism by various drugs the extract of the thyroid gland has no influence on body temperature These observations show that the rise in temperature under the action of the thyroid hormones is conditioned by the augmentation of the oxidative reactions within the organism This is also shown by the changes in the gaseous composition of the blood in thyrotoxicosis, which is also subjected to seasonal fluctuations, as has been shown by P.I. Fedorova /156/. In relation to the discovery of a new, speedier, and stronger acting hormone of the thyroid gland—triiodothyronine—a great number of studies have been made on people as well as on experimental animals, in order to compare its effectiveness with that of thyroxin on the oxygen consumption

It was shown that 3,5,3'—triiodothyronine has, roughly speaking, an effect 3-4 times stronger than thyroxin on the increase of oxygen consumption The peak of the action on basal metabolism of one single thyroxin dose administered intravenously appears on about the 10th day After this the oxygen consumption is reduced, following an exponential curve with a half-life period of about 15 days It was recently reported that it is possible to observe an increase of the oxygen consumption of guinea pigs 4 days after administration of thyroxin. Triiodothyronine administered intravenously in a single dose reaches the peak of its action within 24 to 36 hours and is then reduced, following an exponential curve with a half-life period of about 8 days The thorough study of the comparative action of various triiodothyronine and thyroxin quantities, expressed as the ratio of the general increase in the oxygen consumption $\frac{T_3 \Delta O_2}{T_4 \Delta O_2}$, gave values of 4 to 5 when small doses were given and less than 1 with large doses.

There are reports that ovariectomy augments the sensitivity of female rats to the calorigenic action of thyroxin Thyroidectomized animals withstand anoxia more easily, they demand less oxygen and exhale less carbon dioxide This fact was used as a test for the thyroid hormones, it served to study the life span of animals placed in a closed vessel Thyroxin and triiodothyronine considerably shortened this span /580/

Many works have been made on the respiration of tissue preparations obtained from normal animals, thyroidectomized animals, and animals receiving thyroxin The central nervous system /418/, the muscles, the kidneys, the liver, and the cardiac muscle /585, 201/ showed increased utilization of oxygen after the action of thyroxin and reduced consumption after thyroidectomy.

There are some differences of opinion on the oxygen consumption—the response of tissues to the action of thyroxin— but most tissues, except the brain, the spleen, and the gonads, have a definite response of increased oxygen consumption after the administration of thyroxin.

It has been shown that the absence of the thyroid gland leads to a considerable reduction in oxygen consumption by the brain in humans, although hyperthyroidism has no perceptible effect

Influence on water and mineral metabolism

It has been supposed for a long time that the thyroid gland takes part in the water metabolism of the organism This is seen from the well-known polyuria in hyperthyroid patients and oliguria in hypothyroid ones It is also known that administration of TSH augments the excretion of water from the organism, but this phenomenon is not found after thyroidectomy Other glands of internal secretion which mediate the control of the central nervous system of the water-electrolyte

metabolism participate in the regulation of the water balance. It was already shown in the early works of Eppinger (cit. from M.N. Fateeva,/154/) that thyroidine provokes increased diuresis and that after thyroidectomy the excretion of water from the organism is retarded Thus, for example, after administering 300 ml of water into the stomach of a thyroidectomized dog, the quantity of urine excreted after 3 hrs constituted only 30% of the liquid administered, while in normal dogs it was equal to 61% Normal rabbits excreted 100 ml of water during 80 min, rabbits receiving thyroidine excreted the same amount in 40 min, and thyroidectomized rabbits in 102 minutes.

Clinical observations gave a similar picture Emaciation, abundant perspiration, diarrhea, and the absence of skin infiltration are observed during Basedow's disease, and contrary phenomena during myxedema

The subcutaneous tissue contains 10-65% of water, after thyroidectomy the water content of the skin increases /75/.

S. G. Genes and N. G. Lesnoi /40, 41/studied in detail the capacity of a dog's organism to excrete excess quantities of water, which were administered every 15 min during 4 hrs through a stomach fistula The increase of the hormone quantity of the thyroid gland by feeding a dog with fresh thyroid tissue led to a considerable augmentation of the water excreted Thus, if normal dogs excreted 69-74% of the administered water in 4 hrs, after feeding with thyroid gland this capacity rose by 20-36%, and after total removal of the thyroid gland it was reduced by 33-37%. The same authors showed an increase in the water evacuation from the stomach in 7-19% of the dogs receiving 50 g of fresh thyroid gland daily Total removal of the thyroid gland led to a decrease of the evacuating function by an average of 24%

The mechanism of the disorder of water metabolism in hyperthyroidism has not yet been completely clarified Results exist which confirm the presence of a central mechanism for the evacuation of excess of water from the organism. But in this process, disorders of the rate of metabolic processes and local changes of various metabolic aspects, mainly those of the protein and mineral metabolisms, also have a great importance.

The study of the mechanism of the regulating effect of the thyroid gland on the evacuation of an excess of water from the stomach showed that this action of the thyroid hormones is controlled by the central nervous system, as during medullary narcosis the effect of the thyroid gland on the evacuating function of the stomach was considerably weakened

Thus, according to the results of S. G. Genes and N. G. Lesnoi /41/, the evacuating function of the stomach depends on the influence of the nervous system as well as on the effect of the thyroid gland hormones, this dependence is much more expressed in the first case than in the second But, upon prolonged lack of thyroid gland hormones in the organism, the evacuating function of the stomach is weakened almost to the same extent as during inhibition of the central nervous system in normal animals

It is known that the posterior lobe of the pituitary, secreting an antidiuretic hormone, has an important role in regulating the water metabolism of the organism But the experiments of Swann and Johnston /556/ on rats with diabetes insipidus, caused by the removal of the posterior lobe of the pituitary and augmented by administration of a saline solution, showed that under these conditions the functioning of the thyroid gland was normal Thyroidectomy before removal of the posterior lobe of the pituitary caused only a weak development of diabetes insipidus The administration of thyroid gland preparations did not have any effect on the metabolism of fluids of these rats.

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in hyperthyroid patients Similar results were later obtained in experiments on rats, upon giving them dessicated thyroid gland A series of researchers showed that if hyperthyroid patients are maintained on a diet with a low calcium content they excrete it to a larger extent than healthy people and that, in general, hypothyroid persons show a tendency to excrete less calcium than healthy ones

New studies making use of thyroxin and triiodothyronine also could not determine a constant and homogeneous effect of thyroxin and triiodothyronine on the calcium metabolism /189/, and during experimental changes of the thyroid gland activity no definite fluctuation of the calcium blood level was noted A series of studies has recently been made on the relationship between thyroxin and magnesium in the metabolic processes It has been shown that the demand of the organism for magnesium is augmented in thyrotoxicosis In thyrotoxic rats its level in the serum is lowered /319/ The augmentation of the demand of the organism for this element during the action of the thyroid hormone is possibly related to the interaction of magnesium and thyroxin in their action on oxidative phosphorylation It is known that the uncoupling of oxidative phosphorylation by thyroxin is prevented by adding magnesium /319/ Reports have been published on the increased binding of the serum magnesium in hyperthyroidism and on the reduction of its level in myxedema /265/ But, according to the results of other authors, patients suffering from hypo- and hyperthyroidism do not exhibit any considerable differences in the content of general, as well as of ultrafiltered magnesium of the serum, as compared to healthy people /243/.

The metabolism of phosphorus is probably more influenced by the thyroid hormones Thyroxin and triiodothyronine provoke a loss of phosphorus in the urine and feces /189/ The source of this phosphorus is unknown, but the thyroid gland has no influence on the level of phosphorus in the blood Grinberg and his coworkers (cit from Kheveshi, /159/) noted that hyperfunction of the thyroid gland influences the rate of the P^{32} cycle, while there are no noticeable changes in the total of the phosphorus fractions The content of P^{32} in the acid-soluble inorganic or labile fractions of the liver or kidney phosphorus of rats in hyperthyroidism, 10-100 min after the administration of radioactive phosphorus, was 25-30% lower; in the muscles it was more than 100% higher than in starved control rats It was also found that in hyperthyroidism the accumulation of P^{32} in the blood, liver, and kidneys is increased, and that in the muscles it is reduced During this time the liver had the strongest activity in relation to blood and the muscles had the lowest On the other hand, the ratio of specific activity is considerably higher in the muscles of hyperthyroid animals and this is probably related to a speedier absorption of P^{32} The increase of the absorption rate of P^{32} in hyperthyroidism may explain its relatively low content in the blood, liver, and kidneys

The determination of the specific activity of the P^{32} ratio in the composition of organic muscle compounds to the specific activity of the inorganic P^{32} of the blood of thyrotoxic rats who received 500 μC of $NaH_2P^{32}O_4$ showed higher values than the control animals /372/, which points to a higher rate of the P^{32} incorporation in the muscles during thyrotoxicosis But the analysis of the organic phosphorus ratio of the muscles to the inorganic phosphorus inside the cells revealed a slowing down of the synthesis of organic phosphorus compounds in the experimental animals The ratio of the P^{32}, included in an organic compound, to the O_2 consumed was also found to be lower in rats with thyrotoxicosis than in normal ones The ratios determined in these experiments show that the thyroid gland acts on the rate of phosphorus transfer through the cellular membranes

The inclusion of radioactive phosphorus in the various tissues of rats,

In hypothyroidism edemas are more mucous and are related to disorders of metabolic processes A disorder of the protein metabolism, which takes place in thyroid pathology, leads to the reconstruction of the colloid structure of the connective tissue, not only to the accumulation of the glucoprotein mucin, but also to changes in the hydrophilic nature of the colloids, as a result of continuous water retention It is possible that a disorder of the lipoid metabolism also has a certain importance Mucin, having a strong hydrating capacity, is the basic material which retains water and the retention of glycogen and minerals augments the accumulation of water in the tissues

The changes of water metabolism, which set in during functional disorders of the thyroid gland, are constantly combined with disorders of the mineral metabolism It has been determined by numerous studies that the thyroid gland hormones are involved in the metabolism of a large number of mineral elements Eppinger (cit from M. N. Fateeva, /154/), already pointed out the role of the thyroid gland hormones in the metabolism of sodium chloride. According to his results, the excretion of sodium chloride in hyperthyroid dogs was, after loading with hormone, 47% higher than in normal ones and it occurred very slowly after thyroidectomy.

According to the majority of studies made recently, thyroxin and triiodothyronine also have a constant effect on the excretion of chlorides in urine; but there are also contradicting results

Preliminary adrenalectomy removes the action of the thyroid gland on the metabolism of sodium chloride Consequently, the hormones of the thyroid gland do not act directly on the mineral metabolism, but their influence is mediated by the adrenal cortex through mineral corticoids and, probably, also by changing the activity of the posterior lobe of the pituitary The latter contains an antidiuretic hormone and a diuretic hormone is contained by the adrenal cortex A weaker or stronger stimulation of both glands by iodothyronines and a "play" in the extent of activation of both also gives a direct effect It has been shown that the content of chlorides in the perspiration of hyperthyroid patients is lower and in the more severe forms of hyperthyroidism their excretion in the urine is also reduced

According to the research of other authors, the effect of the thyroid hormones on the excretion of potassium is not constant Thus, Bear (cit from the book The Hormones, /358/) reported that in hypothyroid or in healthy people large doses of thyroxin provoke the loss of these elements, while the excretion of sodium by hypothyroid people was more considerable than that of potassium, more sodium is lost by normal persons He concludes from this that the liquid accumulated by patients suffering from myxedema is extracellular In healthy people a strong thyroxin effect also provokes the loss of intracellular water and salts

In this connection attention should be paid to the paper by S. Ya Kaplanskii [illegible] -ter- [illegible] -nt [illegible] n- fluence on the potassium, calcium, and chlorine contents of the skin [illegible] of thyroxin and triiodothyronine [illegible] increase of [illegible] tissue origin upon administering thyroidine

The influence of the thyroid gland hormones on the metabolism of calcium is not clear enough. An initial increase of the calcium excretion in urine was observed

of nitrogen is accompanied by a surplus diuresis of potassium, while in patients suffering from myxedema an increased quantity of sodium is excreted with the nitrogen in urine. This confirms the view that nitrogen excreted during myxedema is of an extracellular source

The thyroid gland hormone enters into the intimate mechanisms of the creatine and creatinine metabolism It has been known for some time that in Basedow's disease creatinuria is constantly observed, as well as a reduction of the creatinine excretion, which is related to it. In hyperthyroid patients the tolerance to creatine is reduced, as compared to healthy persons The same picture is observed in experimental animals Severe creatinuria is observed after the administration of thyroid preparations A reduction of creatine and creatine phosphate was noted in the muscles of a rabbit which received thyroid gland hormones, and their augmentation was noted after thyroidectomy But such an action of thyroxin is not considered as being specific, for insulin and adrenalin have an analogous effect, reducing the quantity of creatine in the cardiac and skeletal muscles. But creatinuria provoked by adrenalin does not appear during thyroidectomy.

The source of augmented creatinuria was studied by a number of authors The exhaustion of glycogen during hyperthyroidism may be a factor which augments creatinuria, as this was observed during starvation It is known that morphologic and metabolic changes occur in the muscles during hyperthyroidism, reminiscent of the picture of progressive muscular dystrophy The observations of Bodansky /223/ show that an injection of thyroxin to rats leads to the reduction of muscular creatine by 20-40%,and of the creatine of cardiac muscle by 40-50%, as compared to its normal content

It was found that thyroxin or TSH, administered to intact animals, provokes the loss of the accumulated creatine and does not enhance its synthesis The reduction of the in vitro creatine synthesis by liver sections, from rats fed with dessicated thyroid tissue, as well as the enhancement of its excretion, show that the excretion of creatine really occurs at the expense of the existing reserves of tissue creatine

Mongdal and others /427/determined that hypothyroidism provoked by methylthiouracil leads to the reduction of creatine excretion and stimulates its synthesis in liver tissue These authors also think that the excretion of creatine in thyrotoxicosis is conditioned by the suppression of its phosphorylation There is proof that during a hyperthyroid state a reduction of ATP by 25-50% occurs in the heart The augmentation of the creatine excretion does not depend on its increased production, but rather depends on defects in its utilization and may be related to the reduction of creatinine excretion

According to Lippman /397/, and the experiments of Borsook and Dubnoff /227/, the main method of creatine metabolism is its transformation, with the participation of ATP, into creatine phosphate, with subsequent dephosphorylation into creatinine Consequently, the absence of ATP could be the cause for the loss of the capacity to convert creatine into creatinine Another explanation of creatinuria may be given, following the recent report of Askonas /188/ the enzyme creatine phosphokinase, catalyzing the transfer of phosphate between ATP and creatine phosphate, may be supressed in vivo as well as in vitro

Sure and co-workers /555/ could not confirm published reports stating that 40 mg of ascorbic acid administered daily suppress creatinuria provoked by thyrotoxicosis in rats, or that large doses of a vitamin A preparation prevent the loss of creatine in the myocardium of thyroidectomized rats These authors reported on the possible protecting importance of a diet with a high content of fats and the vitamin B complex against the loss of muscular creatine in rats treated with thyroxin The

2-24 hrs after administering $KH_2P^{32}O_4$, was studied by us in normal, hypo-, and hyperthyroid animals

The above studies /148/, on the distribution of P^{32} activity between the lipoid, acid-soluble, protein, and nucleic fractions in healthy, hypo-, and hyperthyroid rats, showed that in animals receiving thyroidine for a long period a higher activity of the lipoid and nucleic phosphorus is observed 24 hrs after administering KH_2PO_4, and the activity in the fraction of inorganic phosphate is reduced. Rats possessing a thyroid gland destroyed by radioactive iodine differed little from normal animals in the distribution of phosphorus in the various fractions Besides, an unequal distribution of the phosphorus fractions in the various organs attracted our attention during hypo- and hyperthyroid states Evidently, more detailed research, with the separation of each component of the acid-soluble and lipoid fractions in the various organs, is necessary in order to judge the action of the thyroid hormone on the distribution and metabolism of phosphorus in the organism

Mandel and Revel /413/ also discovered an augmentation of the P^{32} incorporation into the RNA of the kidneys of rats receiving thyroxin and the rate of its incorporation was higher than the increase of the nucleic acid content.

Studies were also made on the influence of prolonged daily administration of 10 μg thyroxin to rats on the quantity of ATP, of creatine phosphate, and of inorganic phosphate in the cardiac muscle These phosphorus fractions were reduced by the action of thyroxin, but they rose again almost to normal upon administration of ATP /417/ Milcu, Potop, and Ciocerdia found a decrease of the ATP and creatine phosphate contents and an increase of the inorganic phosphate content in the brain of rats to which a single dose of one mg thyroxin, or 250 μg had been administered every two days for 30 days /423/ Consequently, thyroxin augments the utilization of ATP in the cells and its decomposition, with formation of inorganic phosphate

During the last years, a large number of studies were devoted to the problem of the effect of the thyroid hormones on oxidative phosphorylation. But this question is related to the mechanism of action of the thyroid gland hormones and will be examined further on The thyroid gland also has an effect on the metabolism of iron Thyroidectomy in rabbits provokes a rise of the iron level in the serum by 25%, compared to its content in a normal animal, and leads to a certain reduction of it in the tissues Thyroxin re-establishes the normal level of the iron content.

Austoni, Zilliotto, Odeblad /196/ administered Fe^{59}-labeled iron citrate intraperitoneally to thyroidectomized rats and determined that in these animals the level of iron in the bone marrow and the blood as well as the radioactivity were lower than in the control rats, while they were higher in the spleen and in the liver After administration of a thyroid gland extract, iron metabolism in the bone marrow of thyroidectomized rats speedily recovered /195/

Action on the metabolism of nitrogen substances

Administration of thyroxin has an influence on the various aspects of nitrogen metabolism The nitrogen balance is frequently considered as being the only indicator of a disorder of the nitrogen metabolism The change of the rate of metabolism, appetite, and absorption of nitrogen from the intestine are very evident A negative nitrogen balance becomes established in healthy people by the action of thyroxin, and this is confirmed by the increase of nitrogen excretion in urine

of nitrogen is accompanied by a surplus diuresis of potassium, while in patients suffering from myxedema an increased quantity of sodium is excreted with the nitrogen in urine This confirms the view that nitrogen excreted during myxedema is of an extracellular source

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favorable effect of such a diet is related by these authors to a possible sparing effect of the fats on protein metabolism Subcutaneous injection of glycine led to a slight augmentation of the excretion of transformed creatine in urine and to a considerable augmentation of the excretion of creatinine. But also glycine could not prevent a great loss of creatine from the muscles and the myocardium.

Vitamin B_{12} weakens the negative balance of nitrogen in hyperthyroid rats receiving thyroxin There are hypotheses on the fact that vitamin B_{12} leads to a protein economy in the organism and that this vitamin may interfere in the action of thyroxin on metabolism It is known that vitamin B_{12} reduces the growth inhibition caused by thyroxin and also reduces disorders in the utilization of proteins for growth The augmented demand for vitamin B_{12} in thyrotoxic animals is well established, and so is the reduction of the vitamin B_{12} reserves in the tissues of animals receiving thyroxin Magnesium is also included in these interrelations /319/

It was also noted that castration following thyroidectomy increases the creatine content of urine But creatinuria may also be caused by thyroxin in the absence of a thyroid gland, a thymus gland, or a gonad

Sure and others /555/ also showed the influence of the thyroid hormones on the distribution of nonprotein nitrogen in the blood and the urine. They administered a daily dose of 0 5 mg of dl-thyroxin to rats for 5 days and then increased the dose to one mg and continued the administration for 12-14 days A disorder of the nitrogen metabolism was determined, which was proved not only by the increase of the excretion of total nitrogen and by considerable creatinuria with reduction of the transformation to creatinine, but also by the increase of ammonia and uric acid and by a noticeable reduction of the allantoin excretion The change of the ammonia nitrogen was at the same time + 132 2%, that of uric acid +44.7%, that of transformed creatinine -42 9%, that of allantoin -15 6%, and that of creatine +125% The excretion of allantoin was reduced during the last week of the experiment

In hyperthyroid animals on a diet of high carbohydrate content, and in thyroidectomized animals on a mixed diet, a more intensive excretion of nitrogen in urine was observed than in control animals. In thyroidectomized animals the level of urea in the blood was higher than in control ones A considerable accumulation of uric acid in the blood was found in animals receiving thyroxin In people receiving thyroxin there were no changes in the uric acid blood level, but there may be a reduction of it in the urine No changes in the excretion of purine metabolism products were observed in thyroidectomized persons In a number of other studies an increased excretion of urates was discovered Thus, for example, Bertola and Curzio /217/ determined that thyroxin brings about an increase of uric acid excretion and especially of allantoin, in rats kept on a nonnitrogenous diet

The increase of amino acids of the plasma, which is observed after removal of the viscera of rats, is even more noticed upon administering thyroxin, and is reduced by thyroidectomy This emphasizes that the catabolic role of thyroxin in nitrogen metabolism is more sharply expressed than its effect on the enhancement of deamination and on the synthesis of urea

Thorough studies were made by E. A. Dergousova /52, 53/ on the change of nitrogen metabolism during blockade of the thyroid gland by 6-methylthiouracil in rats and mice, as well as in hyperthyroidism in persons She determined the reduction of the $\frac{\text{albumin}}{\text{globulin}}$ coefficient in the serum in hyperthyroidism in relation to the

increase of globulins. According to her report, made together with S. E. Epel'baum, an augmentation of the level of nonprotein nitrogen in the blood of rats is observed in hyperthyroidism /172/. The increase of the residual nitrogen is explained by the enhancement of proteolysis in the tissues and by the increased activity of the proteolytic enzymes. Studies made by E. A. Dergousova, as well as reports by Sheves, Epel'baum, and Ryumina /169/, show that in hypothyroidism the rate of inclusion of methionine in the tissue proteins is reduced.

M. M. Smyk and L. Ya Fishchenko /133/ showed a reduction of the urea formation in the liver of rabbits with experimental thyrotoxicosis These animals excreted an administered dose of ammonium carbonate in the form of urea, which was 25% less than that in control animals

The thyroid hormones act on nitrogen metabolism not only by increasing the rate of dissociative processes, as may be seen in relation to carbohydrate and lipid metabolisms The influence of thyroxin on growth also implies its influence on synthetic processes. Whether the hormone of the thyroid gland is mainly anabolic or catabolic depends to a considerable extent on its dose and on the metabolic state of the organism at the time of the hormone administration According to the results of R. I. Salganik /120/, the mode of action of the thyroid gland hormones on protein metabolism is also determined by the quantity of proteins that enter the organism When enough proteins are included in the food thyroxin reduces the formation of protein in the organism, possibly enhancing their dissociation Blocking of the thyroid gland reduces the protein synthesis When proteins are normally included in the food and the secretion is normal thyroxin enhances the synthetic processes The administration of thyroidine to rats kept on a low protein diet enhanced the protein synthesis and increased their accumulation in the liver An increased utilization of proteins administered to the organism of previously starved rats was observed In hyperthyroid rats receiving heavy water a higher concentration of deuterium was observed in the liver than in control animals /375/ and this also points to the enhancement of the synthetic processes

Hoberman and others (cit from The Hormones , /358/) determined by means of N^{15}-labeled glycine that the rate of protein catabolism in thyroidectomized rats is reduced, while the catabolism of amino acids reaches such extents that a negative nitrogen balance ensues. The rate of the protein synthesis in thyroidectomized and control rats is identical Similar results were obtained in our study on the rate of the labeled methionine incorporation into the tissue and blood proteins of thyroidectomized rats /147/

Liver sections of thyroidectomized rats liberate less amino nitrogen from added amino acids than those of normal rats. A. V. Azyavchik /3/, studying the activity of liver d-amino-oxidase of rats, kept on a low protein diet, determined that the reduction of the activity of this enzyme is speedily restored upon the addition of thyroidine to the diet of the rats.

Changes of the blood proteins are also discovered in pathology of the thyroid gland It was noted th., an increase of the globulin fraction of the blood and a certain rise of the total serum proteins occurs during myxedema, at the same time, administration of thyroxin lowers the blood-protein level, increasing the globulin expenditure. During myxedema the cerebrospinal fluid also contains more protein than the blood. Such changes in the protein content of the blood were also observed in various types of experimental animals.

The distribution and quantity of I^{131}-labeled albumin was also studied on euthyroid persons /508/ During the period of administration of the thyroid gland preparation there occurred a decrease of the general concentration of the blood serum proteins, with a simultaneous decrease of the albumin and globulin concentration

But, as an augmentation of the total volume of the plasma was observed at the same time, the quantity of intravascular albumin was not reduced All persons exhibited an increase of the metabolic dissociation of albumin during this period, and this was shown by the increase of the I^{131}-excretion in urine. But, according to the opinion of Rotschild, Bauman, Yalow, and Berson /508/, this is only compensated to a small extent by the augmentation of the albumin synthesis

Protein nitrogen of the kidneys of rats receiving thyroxin is increased, although these nitrogen substances were also increased by the action of thiouracil It follows from this that thiouracil either enhances the protein synthesis or represses its metabolism Thyroidectomized rats contained less protein and more fats in their organism than control animals /523/ In these animals the liver and kidney weights were reduced, and so were the total and relative quantity of proteins in both organs The liver protein was augmented in rats under the action of thiouracil, as compared to control animals, on the other hand, thyroxin increased the liver weight as well as the protein content /550/.

Thyroxin does not lead to a negative nitrogen balance in adrenalectomized rats During experimental burns, when there is a high negative nitrogen balance, thyroidectomy does not restore the normal nitrogen balance in the organism It is rather the adrenal glands than the thyroid gland which have a decisive negative action on the nitrogen balance in the presence of burns /525/

A large number of works have recently been made in order to clarify the role of the thyroid gland in the metabolism of nucleic acids It was found that administration of thyroxin increases the quantity of RNA and DNA in the liver, kidneys, spleen, and pancreas of rats and that thyroidectomy reduces them. A thiouracil dose has an analogous effect to thyroxin; therefore a complementary effect of this compound is assumed, besides the capacity of reducing the formation of thyroid hormones

Augmentation of the protein and RNA in the kidneys of rats receiving thyroxin was also noted in the experiments of Mandel and Revel /413/ Upon studying the P^{32} incorporation rate into RNA, it was determined that the entrance of phosphorus into the composition of nucleic acid is higher in quantity than the absolute increase of RNA content

Upon studying the changes of the RNA content of the salivary glands of hypophysectomized and thyroidectomized rats, it was found that after hypophysectomy the RNA content of the acinary cells is sharply reduced, while administration of 10 μg thyroxin combined with 200 μg testosterone leads to the normalization of its level. Inhibition of the thyroid gland function led to a reduction in the RNA content of the acinary-cell plasma of the submaxillary and sublingual glands, but did not change its quantity in the parotid gland /222/.

Gugenheim et al. /335/ studied the level of RNA, nitrogen, DNA, and pteroylglutamic acid in the liver of hypo- and hyperthyroid rats and discovered a reduction of the RNA content in hypothyroidism No perceptible changes were noted in the other components. The authors came to the conclusion that the metabolism of RNA and DNA does not depend on the metabolism of folic acid.

The metabolism of other nitrogenous substances is also related to the thyroid gland In hyperthyroid patients there is a decrease of the blood glutathione level, [illegible] administration of thiouracil or radioiodine [illegible] e are studies on the reduction of the synthesis [illegible] xin interferes with the metabolic processes [illegible] for example, that upon including thyroid

hormone in the diet the oxidation of tyrosine in liver homogenates was inhibited by 75% /398/. It was shown by in vitro experiments that the thyroid hormones suppress the oxidation of tyrosine not in a competitive manner, but by reducing the rate of its transamination with α-ketoglutaric acid

The experiments show that, as thyroxin, triiodothyronine and diiodothyronine also have the capacity of inhibiting the tyrosine oxidation, but the action of the iodotyrosine is competitive. The reduction of the intensity of alanine oxidation by liver and kidney homogenates of rats, which had previously received an injection of thyroxin, was also established in the works of Ratliff /468/.

Action on the metabolism of carbohydrates

There are fewer studies on the action of the thyroid gland hormones on the processes of digestion, carbohydrate absorption, and glucose utilization in the organism, than works devoted to clinical observations on glycemia in patients suffering from thyroid pathology

The hormones of the thyroid gland enhance the processes of carbohydrate catabolism. During thyroid insufficiency the absorption of glucose from the intestine is reduced, this possibly explains the high tolerance to glucose of hypothyroid patients and thyroidectomized animals. A decreased tolerance to sugar is characteristic of hyperthyroidism Excretion of sugar in urine is noted in patients suffering from thyrotoxicosis when its level in the blood is higher than 150 mg% /96/.

Thorough studies have shown that besides glucose there is also an increase of the xylose and galactose absorption from the gastrointestinal tract of rats receiving dessicated thyroid tissue /184/. The influence of thyroxin on the galactose absorption from the intestine of dogs was studied at various time intervals after the administration. Upon giving thyroxin daily the absorption of galactose increased during the first seven days, after 14 days this capacity was reduced, and after 20 days it returned to the previous state /326/. During the study attention was also paid to the fact that stilbestrol, administered together with thyroxin, considerably raises the galactose absorption rate and causes its accumulation in the blood. There are studies showing that the administration of small doses of thyroid hormone leads to a better assimilation of galactose, but large doses of thyroxin have a negative effect on the assimilation of galactose, which is in general fixed and assimilated to a considerably lesser extent by the tissues. Glucose administered intravenously to a hyperthyroid man is normally metabolized. In a hyperthyroid animal overdosing with glucose raises the blood sugar and thyroxin itself enhances the hyperglycemic reaction of the organism to the administration of adrenalin and to other influences raising the level of the blood sugar /96/. Some proof of the increase of the glucose-utilization rate by the thyroid gland has also been brought. This was noted in relation to the fact that blood sugar of eviscerated animals falls off faster during hyperthyroidism than in similar animals having a normal thyroid gland. There are also reports on an increase in the absorption of pentose from the blood under the influence of thyroxin.

The influence of thyroxin on the tissue decomposition of carbohydrates was studied on the organism as a whole as well as on tissue preparations.
T.I. Larionova /87/ studied the carbohydrate-phosphor oxidative metabolism in the liver and skeletal muscle during experimental thyrotoxicosis of rats. She determined the lowering of aerobic as well as anaerobic phosphorylation in the liver and an increase of the O_2 utilization. She noted a disorder of the formation of labile phosphorus in skeletal muscle as a consequence of the inhibition of phosphate transfer from ATP to creatine. There was no disorder of the carbohydrate-phosphor metabolism in the muscles of animals receiving thyroxin. The accumulation

of fructose diphosphate was increased in relation to its formation. It was shown that muscle glycolysis is augmented by the action of thyroxin. Thus, for example, I.I. Kotlyarov /85/ determined an enhancement of amylolysis in extracts of liver tissue after the injection of thyroxin to rabbits, as well as upon adding the hormone in vitro. This effect of thyroxin was attributed to its influence on the activity of liver glycogenase, but in view of the fact that thyroxin has no action on pancreatic amylase, the author explains the enhancement of amylolysis in the liver by the action of the hormone on the phosphorylase.

Upon adding yeasts to a thyroxin medium, or to extracts of thyroid gland, an increase of the sugar fermentation was noted /96/.

At the same time, observations were made /405/ on hypo- and hyperthyroid patients in whom an increase of the glucose utilization rate was determined after thyroidectomy on the basis of the accumulation and clearance coefficient in hypothyroidism in general and after overdosing with glucose. In hyperthyroidism the utilization of glucose was maintained on a normal level.

As a result of increased glycolysis an augmentation of the lactic acid quantity in the blood is noted in animals. After thyroidectomy lactic acid in the blood was reduced. The lactate content of the blood rose to a lesser extent after the action of adrenalin on thyroidectomized animals than in normal ones.

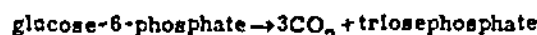
There is also evidence on the increase of the pyruvic acid content of the blood in experimental hyperthyroidism. Recent works of Siedek and Hein-Sekula /530/ on the influence of thyroxin on the metabolism of fructose and galactose in people, showed that overdosing with fructose leads to reactive hypoglycemia, which is accompanied by a lowering of the pyruvic acid content of the blood. Thyroxin reduces the assimilation of galactose by the organism. After overdosing with galactose the quantity of sugar and its excretion in the urine remain high for a considerable time under the action of thyroxin.

Works have recently been performed on tissue preparations in order to throw light on the glycolytic rate and on the oxidative phase of the carbohydrate metabolism under the action of thyroxin in various organs. The results obtained prove that in all cases these processes are speeded up by the thyroid hormones. Thus, the research of Comsa /247/ demonstrated the speeding up of the glucose utilization by isolated rat diaphragms.

Macho /404/ determined the glycolytic activity of the blood by the reduction ... content after incubating at 37° for 6 hrs without any additions and
... ound
... zed
rabbits glycolytic activity is considerably lower; after adding thyroxin it increases and rises above the level observed in intact animals.

I. Potop /114/ studied the action of thyroxin in a prolonged experiment on ... in the brain of rats, and discovered a reduction of the
... g-
... f the thyroid hormones on the ...

As is known, it has recently been proved that, together with a glycolytic cycle, there also exists a complementary mechanism of monosaccharide transformation into pyruvic acid. This second method of carbohydrate transformation, discovered in plants and animal organisms, was called the phosphogluconate method or the hexose monophosphate shunt /104/. Thorough study of the various reactions and enzymes of this system made it possible to give a structural scheme of the oxidation method of monosaccharides, which begins with glucose-6-phosphate and leads to the formation of one molecule of triosephosphate with the liberation of 3 molecules of CO_2. The phosphogluconate reaction by which monosacharides are degraded can be summed up by the following formula:



glucose-6-phosphate $\rightarrow 3CO_2$ + triosephosphate

At the beginning of this reaction glucose-6-phosphate by the action of glucose-6-phosphate dehydrase and the required participation of triphosphopyridinenucleotide (TPN^+) forms glucose-6-phosphate, glucose-β-lactone, and then 6-phosphogluconic acid. Under the action of dehydrase and TPN^+ this acid forms 3-keto-6-phosphorgluconic acid which, when the first carbon is removed in the form of CO_2, is transformed into 5-phospho-ribulose.

Thus, if during the glycolytic degradation of glucose to CO_2, according to the cycle of Embden and Meyerhof, the carbon atoms 1 and 6 become metabolized at the same rate, then in the phosphogluconate method C-1 will be transformed by preference This difference is especially noticed if observations are made at short intervals.

Spiro and Ball /536/, comparing the radioactivity of CO_2, after injection of glucose-1-C^{14}, to that of CO_2 after injection of glucose-6-C^{14}, found that in hyperthyroidism both basic ways of glucose metabolism are enhanced. This concurs with the results published earlier on the augmentation of glucose-6-phosphate and 6-phospho-gluconic dehydrase activity in liver extracts of thyrotoxic rats /320/

Dubovsky and others /535/ studied the rate of the hexose monophosphate transformation of glucose on erythrocytes of thyrotoxic patients and on rats receiving thyroxin. They determined the augmentation of the sedoheptulose accumulation, which is a proof of the increase of the glucose metabolism by way of the hexose monophosphate shunt.

There is a number of works concerning the glycogen metabolism under the action of the thyroid gland hormone. Most researchers think that in hyperthyroidism there is a loss of the liver glycogen and this could be based on an augmented dissociation and oxidation of sugar, on an augmented stimulation of the sympathetic nervous system and thus on the sensitivity to adrenalin. But it is considered that the glycogen reserves do not diminish when there is enough sugar in the food. It was determined in experiments with angiostomized animals that the quantity of sugar leaving the liver increases under the action of the thyroid hormone.

In recent works Milcu, Potop, and others /424/ showed an increase of the anaerobic decomposition of glycogen and a reduction of the glycogen content of the brain, which is related to it.

In experiments on rats Bertrand /219/ determined the reduction of the liver glycogen content after administering thyroxin for 4 days, in daily doses of 0.3-1.5 mg. Upon administering blood serum of thyroidectomized horses to these animals, the action of thyroxin on the liver glycogen content was suppressed.

Many authors note that, together with an increased decomposition of the liver glycogen by the action of the thyroid hormones, there is also a disorder of the

glycogen synthesis and its formation from noncarbohydrate predecessors. But the question of the glycogen synthesis has not yet been fully determined. Reports exist according to which experimental hyperthyroidism reduces glycogen formation in the liver of rats fed with glucose. It has also been shown that partial removal of the pancreas of dogs makes them receptive to the action of thyroxin, the administration of which then has a diabetogenic effect. On the other hand, as is noted in a paper recently published by Hedon et al. /348/ the appearance of diabetes was not noted in dogs in which the pancreas was partly removed and who were given daily doses of 0.015 or 0.05 mg triiodothyronine per kg weight for 14 days. Similar studies on diabetic dogs showed that thyroidectomy provoked by radioiodine has no influence on the course of diabetes.

The question of the products at the expense of which the disorder of glycogen formation takes place is also unclear. It was determined in experiments on rats that thyroxin had no effect on the formation of glycogen from lipids and stimulated the transformation of proteins into carbohydrates /182/. The study of the diabetogenic effect of triiodothyronine and of its combinations with other hormones shows that, upon giving triiodothyronine to artificially fed intact rats, it provokes hyperglycemia and glucosuria with loss of nitrogen and loss of weight. Its combination with growth hormone and cortisone leads to a summation of the effect, but not to a synergistic action.

It may be concluded from all that has been said that the thyroid hormones have considerable influence on all the carbohydrate transformation phases in the organism of animals starting from absorption in the gastrointestinal tract and ending with the decomposition of glucose in the tissues and the synthesis and formation of glucose in the liver. All these stages in the carbohydrate metabolism are accelerated by the action of thyroxin. But several questions on the action of thyroid hormones on the stages of carbohydrate transformation remain as yet unclear.

Action on the fat metabolism

It has been known for a long time that human hypothyroidism is almost always accompanied by an increase of cholesterol in the blood. Together with this, an increase of the neutral fat and of phospholipid contents was also noted. The interrelations between hormones of the thyroid gland and lipids have been studied repeatedly with the use of new methods. It may be generally accepted that an inverse relationship exists between the activity of the thyroid gland and the blood content of lipids /89, 419, 420, 454, 455, 303, 304/. But the mechanism of these interrelations remains as yet unclear.

The action of the thyroid gland hormones on the metabolism of fats begins from the absorption process. The absorption of fats in the gastrointestinal tract is increased upon the administration of thyroxin, but too large quantities of the hormone, speeding up the passage of food in the intestine, do not leave enough time for absorption, and this is why it is not possible to note a speeding up of this process in thyrotoxic states. Rosenman and Friedman /505/, studying the lymph of the thoracic duct after administering 100 mg cholesterol to rats, could not determine any considerable changes in its absorption from the intestine of hyper- or hypothyroid animals.

Hyperthyroidism is not always combined with a lowering of the lipids in the blood. It was also determined that a diet rich in fats protects the animals against the lethal effect of large thyroxin doses. Moreover, administration of thyroxin lowers the cholesterol level in the serum of rats on a diet with a high cholesterol content. The study of the general level of lipids, after removal of the thyroid

gland of dogs, and the comparison of these results with the changes of the various lipid fractions led Chaikoff et al. /238/ to the conclusion that, although thyroidectomy leads to the augmentation of all the fractions, the content of the general and the esterified cholesterol is particularly increased. This augmentation sets in at the end of the first week after thyroidectomy and reaches 300 % of the normal content, in most cases it was almost doubled. The rise of the general lipid level usually starts by the end of the first month after thyroidectomy and reaches values 50-90 % higher than the level of the serum lipids before removal of the thyroid gland. Generally, the type of the response of the various lipid fractions to thyroidectomy varies considerably in respect of its extent, the time of beginning, the duration of the given level, and the degree of fluctuation.

According to the results of Strisower et al. /551/, the changes in the blood lipid composition depend on the time of the thyroid gland hormone administration. Prolonged administration of dessicated thyroid gland provoked in humans a reduction of the lipoproteins of the low density group Sf 0-12 and Sf 12-20 and also a reduction of cholesterol in the blood serum during the first weeks after hormone administration. The quantity of lipoproteins of the Sf 0-12 group and of cholesterol later increased and then returned to their initial level after the 24th week. In another work the same authors /552/ obtained analogous results upon prolonged administration of triiodothyronine to patients suffering from psychic disorders.

A series of observations on the action of triiodothyronine and of triiodothyroacetic acid on the level of the serum lipids and lipoproteins also confirm a decrease of the level of these components /272/. Beierwaltes and Ruff /208/ noted a decrease of the cholesterol blood level after administering thyroxin and triiodothyronine to euthyroid persons. But, whereas after ceasing administration of thyroxin the basal metabolism continues to increase and the cholesterol level drops, after ceasing administration of triiodoth[illegible]

level of the serum lipids returned to normal. It was pointed out in the work of Oliver and Boyd /446/ that in euthyroid patients with a myocardial infarction and a high blood cholesterol content triiodothyroacetic acid reduces this content as well as the ratio between cholesterol and phospholipids. But this reduction is not maintained for a sufficient length of time after ceasing the administration of this preparation.

Delmez and Engel /259/ tried to use triiodothyronine for the treatment of hypercholesterinemia. In patients suffering from arteriosclerosis they noted a lowering of the blood cholesterol by 21 %, the initial level was re-established 7 days after ceasing the hormone administration.

Several works have been devoted to the study of the mechanism of fat metabolism disorder under the action of the thyroid gland hormones. In rats the synthesis of the liver phospholipids is reduced by the action of thiouracil and augmented by the action of thyroxin. It was noted that an augmentation of the phospholipid cycle and of nucleic acids occurs in the liver. The excretion of cholesterol in bile is partly controlled by thyroxin and has a definite role in the regulation of the blood cholesterol level. Bile excretion of cholesterol is constantly reduced in [illegible]

[illegible]lesterol synthesis and its destruction and excretion in the intestine was shown in hyperthyroid rats Thus, the reduction of the cholesterol concentration in the plasma in hyperthyroidism is conditioned by its augmented excretion, while the speeding up of excretion is so considerable that even the augmented cholesterol

synthesis is insufficient in order to maintain its normal concentration in the blood. Consequently, it is not the speeding up of the cholesterol synthesis but the augmentation of its excretion which is more characteristic of hyperthyroidism /606, 504/. An inverse picture is observed in hypothyroidism.

The study of the cholesterol metabolism under the action of the thyroid gland hormones showed that the processes of cholesterol synthesis or decomposition are also influenced by the thyroid hormones. When the content of cholesterol in the diet is 0.65 % and when insufficient food is given cholesterol is subjected to an increased decomposition in animals receiving thyroxin. When the cholesterol content of the diet is 0.15 % and a sufficient quantity of food is given the cholesterol synthesis and excretion are augmented /605/.

The processes of cholesterol metabolism were studied by means of labeled acetic acid. An augmentation of the cholesterol synthesis was discovered in hyperthyroidism and a reduction of its rate in hypothyroidism /507/.

Fletcher and Myant /300/ studied the rate of in vitro cholesterol synthesis from labeled acetate and mevalonic acid by liver sections and skin of rats and rabbits receiving thyroxin, or having a destroyed thyroid gland. The authors determined that the cholesterol synthesis is reduced in hypothyroid rats and that thyroxin augments the formation of cholesterol from acetate, by speeding up its transformation into mevalonic acid. It was later noted that thyroxin increases the biosynthesis of cholesterol when it is in low concentrations and suppresses it in high concentrations. The period of the visceral cholesterol cycle is parallel to its synthesis.

Together with the above experiments, which point to an augmentation of the cholesterol biosynthesis under the action of the thyroid hormones, we also find reports that contradict this. Thus, for example, Scaif and Migikovsky /517/, studying the influence of thyroxin and other factors on the cholesterol and fatty acid synthesis by rat liver homogenates, could not determine changes in the cholesterol synthesis by adding thyroxin to the homogenates. Feeding the rats with thiouracil also had no effect on the capacity of the liver homogenates to synthesize cholesterol.

There are some hypotheses that transformation of fats into sugar occurs under the action of thyroxin. Thyroxin, however, apparently prevents the inverse transformation of sugar into fats. Bertolini and Guardamagna /218/ studied the influence of thyroidectomy on the total liver lipid content, upon administering glucose and glucose-1-phosphate. It was found that after administration of glucose, the lipid content in the liver of these animals increases, while after administration of glucose-1-phosphate no augmentation occurs.

Research made by Infante and Turchetto /363/ revealed that thyroxin given to rats which are on a steatogenous diet augments the lipotropic activity of lipocaine and maintains the acetylizing capacity at its normal level.

The role of the thyroid gland in the development of atherosclerosis in man, as well as in experimental animals, has recently been very widely studied. There [illegible] action of triiodothyroacetic acid. It was also proved that patients suffering from hypothyroidism suffer more frequently from atherosclerosis than hyperthyroid and euthyroid patients. As was shown by the experiments of Vitale et al. /599/, thyroxin reduces serum cholesterol, repels kidney affections and re-establishes intimal sudanophilia in animals which are on an atherogenic diet.

M.S. Levchenko et al. /88/ noted, on the basis of experiments by A.B. Shakhnazarov, that iodine, influencing the function of the thyroid gland, prevents the development of atherosclerosis. During experimental hypercholesterinemia in rabbits, M.S. Levchenko and others discovered a reduction by 2-3 times of the I^{131} uptake by the thyroid gland, which is characteristic of an acute hypothyroid state.

However, there are various manifestations of the interrelations between the thyroid hormones and the development of atherosclerosis, which show their great complexity. Recent studies on eight hyperthyroid patients showed the augmentation of cholesterol, and a "normal" development of atherosclerosis was noted after autopsy /517/.

The administration of thiouracil to dogs had no influence on the development of atherosclerosis, but this thyrostatic substance led to the strengthening of atherosclerosis provoked by cholesterol /547/. On the other hand, dessicated thyroid gland protected chicks from the development of atherosclerosis provoked by feeding with cholesterol /255/. In rabbits with experimental atherosclerosis provoked by administration of cholesterol the administration of thyroxin in normal doses did not lead to the regression of the affection.

The thyroid gland and the metabolism of vitamins

Much has been published on the influence of the thyroid gland on the metabolism of vitamins. The study of the interactions between vitamins and hormones is important for throwing light on the effect of vitamins as well as of hormones on the physiological functions of the organism. Notwithstanding the large number of experiments and clinical observations, no clear-cut opinion exists at the present time about the interrelations of the thyroid gland hormones and most of the vitamins, this is why, apart from some exceptions, it is difficult to come to definite conclusions regarding this question As to the interaction between the thyroid gland and vitamin A, studies were made as early as the thirties, which showed that the quantity of vitamin A in the liver and the spleen is reduced after thyroidectomy; it is probable that carotene is not transformed into vitamin A under this condition. Thus, it is considered that thyroxin is necessary for the transformation of carotene into vitamin A /119/.

E.A. Portugal'skaya /113/ studied the influence of thyroidectomy and hyperthyroidism on the carotene and vitamine A content of the liver of rabbits and guinea pigs. She noted a considerable [illegible]
of vitamin A in these animals [illegible]
Upon administering preparati[illegible]
of vitamin A increased and t[illegible] [illegible] content decreased.

Carotene does not prevent a vitamin A deficiency in hypothyroid animals /278, 371, 607/. In those suffering from myxedema the action of thyroxin leads to the rise of the vitamin level of the blood and to the reduction of the carotene content.

But not all authors share the same opinion on the role of thyroxin in the hepatic transformation of carotene into vitamin A.

Arnrich and Morgan /187/ studied the vitamin A content in the kidneys and liver of hypothyroid rats under the influence of thiouracil after administering various quantities of carotene. It was shown that upon administering large doses of vitamin A to hypothyroid rats they accumulated it up to 33 % more than normal rats, upon giving large quantities of carotene also more vitamin A was stocked by hypothyroid rats The analysis of the carotene content of the gastrointestinal

tract could not reveal any differences between normal and hypothyroid rats. The authors conclude that the absorption, transformation, and assimilation of carotene are not directly related to the hormones of the thyroid gland.

Worker /616/ too, could not prove the influence of the thyroid gland on the transformation of carotene into vitamin A. Upon administering 400 mg of carotene to normal, thyroidectomized, and hyperthyroid rats, raised on a diet lacking vitamin A, the vitamin A content of the blood increased in an approximately identical manner in all the animals after 24 hrs. The signs of xerophthalmia disappeared in all the animals.

The influence of vitamin A on the thyroid gland has been studied considerably less. It was noted that an insufficiency of vitamin A, which does not reduce the capture of iodine by the thyroid gland, reduces the inclusion of iodine into thyroxin /607/. On the other hand, there are results which point to the fact that insufficiency *as well as excess of vitamin A, augments the absorption of iodine by the thyroid* gland. It was also pointed out that vitamin A protects animals from an augmented oxygen consumption upon administering dessicated thyroid tissue
N.V. Verzhikovskaya /27/ very recently reported the results of a study on the function of the thyroid gland of rats receiving a complementary dose of 0.14 and 0.7 mg of vitamin A together with an adequate diet. She determined a 2-3 fold reduction of I^{131}-absorption by the thyroid gland, a slowing down of the iodine excre*tion, and a reduction of its quantity in the gland, as compared to control animals.* These results confirm previous opinions about the fact that vitamin A caused a suppression of the thyroid gland function. Further studies showed that vitamin A in large doses reduces the quantity of the thyrotropic hormone in the pituitary of rats /513/.

Reports have been published showing the absence of an activating effect of vitamin A on the function of the thyroid gland. Conte and Stux /248/, administering large doses of vitamin A to guinea pigs, could not note a weakening of the action [illegible]

hormones.

Serfaty and Olivereau /526, 447/, in a series of works, showed by histophysiological studies a lowering *of the thyroid gland activity and the reduction of the* number of β--cells in the pituitary during vitamin A insufficiency.

Some authors are prone to consider the relations between carotene and vita- [illegible] as being anta- [illegible] eight of the [illegible] sm and

vitamin A reduces it.

A number of published results show that vitamin A prevents the loss of glycogen from muscles and liver during the action of thyroxin, that it limits hyperthyroid creatinuria, and that it probably weakens analogous action of the thyroid hormones on the lipid metabolism.

At the same time, there are also results on an increase of the demand of the *organism for* vitamin A in hyperthyroidism. Thus, for example, Wohl and Feldman /612/ determined, by adaptation to darkness, that the formation of vitamin A is disordered in hyperthyroid patients and that its reserves are speedily exhausted. But the opinion on the antagonism between vitamin A and thyroxin was not confirmed in a number of works. Thus, for example, the reduction of the liver glycogen content did not change under the action of thyroxin upon administering

large doses of vitamin A. As N.B. Medvedeva /96/ points out, it is hardly advisable to accept the presence of an antagonism between the above vitamin and the hormone; the interrelation between them is rather determined by the general state of the organism. Hyperthyroidism created by thyroxin provokes an augmented demand for vitamin, related to the general augmentation of metabolism Besides this, a weakening of the carotene fixation and, consequently, of the vitamin A formation is noted during hyperthyroidism.

The augmentation of the demand for thiamine and the augmentation of its excretion in urine was shown in hyperthyroidism /277/. Reports were made on the lack of riboflavin in rabbits with myxedema. The absence of riboflavin in food provoked histological changes of the thyroid glands, without changing the weight of the organ. The demand for riboflavin was also augmented in hyperthyroid rats.

Thiouracil reduces the excretion of methylnicotinamide in urine and this effect is corrected upon administering thyroxin. It is supposed that thyroxin may take part in the methylation of nicotinic acid. But in experiments on rats, upon blocking the thyroid gland with thiouracil, Cherkes /164/ did not find any considerable changes in the excretion of methylnicotinamide after administration of nicotinic acid. Only when loading them with large quantities of nicotinamide was the excretion of the methylated derivative in these animals noticeably smaller than in the control ones. Consequently, hypothyroidism limits the capacity of the organism to methylate nicotinamide only to a certain extent.

On the other hand, vitamins of the B group have a considerable effect on the function of the thyroid gland. S.V. Maksimov and I.N. Sharkevich /91/, keeping rats on a diet lacking in vitamin B_1, determined that the thyroid gland almost totally loses its capacity of absorbing radioactive iodine in vitamin B deficiency. Basal metabolism was also considerably lowered under these conditions. Morphological changes were also discovered in the gland.

The lowering of the function of the thyroid gland under the influence of large doses of pyridoxine was shown in rabbits. Rats which have a vitamin B_6 deficiency take up less oxygen than normal ones P.Ya Siver and others /123/ studied the influence of several vitamins on the absorption of I^{131} by the thyroid gland in rabbits and rats. It was noted that an augmentation of the I^{131} absorption occurs 20 min and 2 hrs after the injection under the influcence of vitamins B_1, B_2, nicotinic acid, and C. The greatest increase of absorption was determined after administration of vitamin C and nicotinic acid A certain enhancement of the I^{131} absorption by the pituitary and the brain was noted in rats under the influence of nicotinic acid. A case of thyrotoxicosis with exophthalmos has been described, whose recovery is related to the use of nicotinic acid /354/, but no explanations are brought for this effect

A number of phenomena bringing to mind the [illegible] of vitamin B deficiency

According to the opinion of N.B. Medvedeva /96/, the enhancement of the vitamin B_1 metabolism during thyrotoxicosis may lie at the root of such a hypovitaminosis, or the demand for vitamin B_1 rises in relation to the general acceleration of metabolism, the latter is more probable and has received a number of experimental confirmations The possibility of accelerating the vitamin metabolism itself is, of course, not excluded

Rubino and Pennetti /509/ found that the administration of thyroxin to pigeons with vitamin B_1 deficiency provokes a considerably smaller augmentation of the demand for oxygen than in the control birds. The liver tissue of avitaminotic pigeons which received thyroxin also gave similar results. The simultaneous administration of thyroxin and thiamine to pigeons with a clear manifestation of beriberi augmented the demand for oxygen in vivo as well as in vitro. The results obtained point to the necessity for vitamin B_1 in some cases, in order to make the effect of thyroxin stand out.

Results on the influence of the group B vitamins on the reactions provoked by the thyroid hormones are contradictory Studies on this question are also few in number. Tipton, Welden, and Weiss /578/ studied the influence of changes of thyroid gland function on the activity of adenosinetriphosphatase and d-amino-acid oxidase in the liver and kidneys of rats under conditions of vitamin insufficiency. They determined that with a defective diet, thyroxin augmented the activity of these enzymes in the liver When the diet was lacking in all the vitamins of the B group, or only in thiamine, the activity of adenosinetriphosphatase did not change, but in riboflavin insufficiency an increased activity of this enzyme was observed in the liver, on which thyroidine had no effect In riboflavin insufficiency the activity of d-amino-acid oxidase was considerably reduced Thyroid preparations had no effect on the oxidase activity of the kidneys, but increased the activity of this enzyme in the liver, not only of those animals which did not lose weight.

There are results about the fact that thiamine prevents the loss of hepatic glycogen, provoked by thyroxin, and that the thyrotropic hormone augments gaseous metabolism in guinea pigs to a larger extent after administering riboflavin than without it.

Thorough studies have been recently made on the interrelations between vitamin B_{12} and the thyroid hormones. Administration of large quantities of iodocaseine to rats provokes a loss of weight and has a lethal effect. Vitamin B_{12} partially protects rats from this effect, but does not suppress the augmented oxygen consumption after administration of the thyroprotein According to other reports, vitamin B_{12} does not protect the organism from thyroxin, but such an effect is obtained by using liver extracts. It was shown by studies on the absorption of radioiodine, that vitamin B_{12} itself has no perceptible effect on the thyroid gland. In rats vitamin B_{12} augments the growth rate and iodocaseine removes this effect. Vitamin B_{12} suppresses in rats the influence of thiouracil on growth, but has no effect on the reduction of the I^{131}-absorption by the thyroid gland, which is caused by thiouracil.

The increased demand for vitamin B_{12} in thyrotoxic animals is a well-established fact. Apart from averting growth inhibition provoked in rats by an excess of thyroxin, vitamin B_{12} also removes disorders in the utilization of protein. In thyrotoxic animals, the reserves of vitamin B_{12} were found to be considerably smaller than in normal ones.

Thus, there is a definite correlation between the actions /319/ of thyroxin and of vitamin B_{12}, but the mechanism of this interaction is as yet unknown.

was 370–390 mg%. A change in the vitamin C content in the organism, as well as a change in its excretion in urine, is noted during pathology of the thyroid gland. Thus, in hyperthyroidism the oxidation of the vitamin is augmented and its excretion in urine is reduced.

T. G. Romanova and D. M. Gorodinskii /117/ noted in most cases a reduction of the vitamin C content in the blood, muscles, and tissues of the thyroid gland in patients suffering from hyperthyroidism. In cases of euthyroid goiter changes of the vitamin C quantity were less considerable.

S. S. Kasab'yan and G. L. Chernyavskaya /77/ determined the content of ascorbic acid in the thyroid gland in goiter and found that its quantity changes depending on the form of goiter, and that it is differently distributed in the epithelium and the colloid of the follicles. According to the results of these authors, the ascorbic acid content is considerable during colloid goiter and the process of its accumulation in the gland is continuous. In a parenchymatous goiter its content is small. In cases of Basedow's goiter ascorbic acid is found in considerable quantities in the colloid as well as in the columnar epithelium of the follicles.

M. M. Eidel'man, M. R. Ozerova, and N. G. Tsarikovskaya /171/ studied the influence of catechin decoctions, having a vitamin P-like effect, on the metabolism of vitamin C in guinea pigs, as well as in persons suffering from goiter under conditions of C hypovitaminosis, provoked by the modification of the thyroid gland function. They showed that after administering vitamin P, the extent of hypovitaminosis C is reduced, but this fact is difficult to explain from the aspect of the interrelations between the thyroid gland and the above vitamins.

4. The Action of the Thyroid Gland on the Activity of Enzymes

The number and types of enzymes which are controlled by thyroxin and other thyroid-active compounds give an idea of the wide range of action of the thyroid gland hormones on the various aspects of cellular metabolism. The action of the thyroid hormones on the various representatives of the oxidizing-reducing enzymes, on esterases, proteases, etc., has been determined by a great number of studies.

An increase of the oxygen consumption occurs in all the tissues under the action of thyroxin and this corresponds to the increase of the activity of a large number of enzymatic systems in the cells. Thyroxin, which augments metabolism, affects first of all the mitochondria, the most important structure of the cell protoplasm, where various enzymes are located and where the synthesizing processes take place. There is more than a score of individual enzymes manifesting the effect of the thyroid gland hormones. The hormonal effect is shown most clearly in the liver, where the enhancement of metabolism by the action of thyroxin as a hormone is most clearly observed.

There is every reason to affirm that, among the various types of enzymes subjected to the action of the thyroid hormones, the oxidizing enzymes are the main target.

It has been possible to show by means of various experiments that an increase of the cytochrome oxidase activity takes place in the liver and muscle tissues after administration of thyroid gland preparations, or in hyperthyroid animals; and on the other hand, its activity was reduced by the action of thiouracil, or in thyroidectomized

rats /275/ But the same method could not reveal an increase of cytochrome oxidase activity in the spleen and brain of hyperthyroid animals Tipton and his co-workers /576/ did not discover an increase of the activity of this very important enzyme in the chain of the cytochrome system in adrenalectomized animals upon feeding them with preparations of thyroid gland

An augmentation of activity of the liver succinic dehydrogenase was also determined in hyperthyroid rats, or in animals after administration of thyroxin /577, 578/ The reduction of the activity of the enzyme was noted after thyroidectomy or after administration of thyrostatic substances No augmentation of the succinate dehydration reaction in brain tissues by the action of thyroid gland preparations was discovered

A number of authors later noted increased activity of d-amino-oxidase, after feeding rats with thyroid gland /380/ A. V. Azyavchik /3, 4/ studied the influence of the thyroid gland hormones on the deamination process in the liver of animals which were on a low protein diet She determined that the deamination process of amino acids in the liver is sharply disordered in rats on protein-deficient diet, and it recovers with difficulty upon transfer to a diet sufficiently rich in protein; it speedily returns to normal upon administering thyroidine in the food.
I. Tsitovskaya /160/ also reports the augmentation of d-amino-acid oxidase activity in the liver under the action of thyroxin She found that under these conditions an increase of the amino acid synthesis from ammonia and ketoacids occurred. An inverse picture was noted in hypothyroidism. Thus, for example, Cagan and others /233/ report the reduction of the activity of this enzyme in thyroidectomized rats But there are results according to which the formation of amino acids from pyruvate and ammonia was reduced, not only after thyroidectomy, but also in hyperthyroidism /235/

Among the other oxidizing enzymes, attention was paid to the reduction of liver lactic-dehydrase activity of rats receiving thyroid hormones and to the augmentation of its activity upon administering thiouracil /596/ The reduction of activity of xanthine oxidase of the liver, which appears as a result of a diet poor in proteins, is avoided by administration of thyroxin

The thyroid gland has a stimulating effect on a large group of *esterases* Various authors determined the activating effect of thyroid preparations, or of a hyperthyroid state, on the cholinesterase of the human blood serum, on alkaline phosphatase of the femur, liver, kidneys, intestine, and thyroid gland of rats and of human blood serum, and on acid phosphatase of the liver, kidneys, and small intestine of rats

Thyroidectomy or administration of thiouracil have in most cases an inverse effect This is shown by the change of activity of human serum cholinesterase and alkaline phosphatase, and by the reduction of activity of the latter enzyme in the intestine, liver, kidneys, and thyroid gland of rats, and in the kidneys of guinea pigs

But not all the results of the various authors concur. Thus, for example, according to some authors, the activity of alkaline phosphatase of the liver tissue is reduced to a considerable extent in hyperthyroidism, and that of serum phosphatase is increased.

There are contradicting results on the activity of adenosine triphosphatase. Venkataraman et al /592/ reported the enhancement of ATP metabolism during [illegible] other researchers could not

ie

There are isolated reports on the augmentation of activity of a number of other enzymes. Thus, amylase, arginase, cathepsin of the liver, hexokinase of the skeletal muscles of rats were found to be more active in hyperthyroid animals, or under the action of the thyroid hormones.

A number of reports have recently appeared on the augmentation of the coenzyme A content under the action of thyroid hormones It is assumed that thyroxin participates in the synthesis of this cofactor, ensuring the acetylation process In a recent survey Yu. A Serebrovskaya /122/ summarized the results published on the interrelations between the endocrine system, coenzyme A, and pantothenic acid. As is noted in that article, acetylation of sulfonamides in animals with a blocked thyroid gland is augmented, and it is reduced when there is an excess of thyroxin It was found that this depends on an insufficiency of acetate. Feuer, Boross, and Kepeks /294/ reported analogous results They determined the inhibition of the acetylation reaction of para-aminoazobenzol by enzymes of the acetylating system from the livers of pigeons upon adding thyroxin and triiodothyronine Substance 3, which they discovered in the thyroid gland, stimulated this process. ATP also participates in the acetylation reaction and the change of its quantity, related to this reaction, is smaller in the presence of thyroxin and triiodothyronine There are hypotheses that thyroxin itself forms an active combination with coenzyme A

5 The Problem of the Form of the Thyroid Hormones Acting at the Cellular Level

Although it has been precisely determined that thyroxin is the main circulating form of the thyroid hormones, there is however, some evidence to the effect that, in order to take on its full activity in the peripheral tissues, it must be transformed into other substances. The most important points of this evidence are a) a long period elapses between the administration of thyroxin and the appearance of a notable change of the basal metabolism, b) the fact that the biological activity of some thyroxin analogues is not suppressed by components antagonistic to thyroxin /409/; and c) the speedier reaction of humans to triiodothyronine than to thyroxin /189/. Hetzel et al /351/ recently studied the initial effects of triiodothyronine and thyrotropic hormone after their administration to healthy persons, they noted differences in the response of the organism. This enabled them to express the opinion that there existed another hormone of thyroid origin, having an immediate effect Such results lead to the conclusion that the hormonal activity of the thyroid gland may be provoked not only by its secretion products, but also by substances arising as a result of cellular transformation of the secretion products of the thyroid gland

Observations showing that 3, 5, 3'–triiodothyronine has a speedier action on intact animals than thyroxin correspond to the above This is why a number of scholars accept the deiodination of thyroxin into triiodothyronine in the peripheral tissues as the first stage of formation of an active form of the thyroid hormones at the cellular level But, as has already been noted, no one succeeded in determining the transformation of labeled thyroxin in the peripheral tissues, except for the kidneys /180, 253/ Besides this, administration of triiodothyronine to intact animals also has no immediate effect. Barker /199/ could not determine augmentation of the oxygen consumption by the tissues of the spleen, brain, stomach muscles, uterus, and thyroid gland of thyroidectomized rats under the action of triiodothyronine. Thyroxin also had no effect. The author concludes from this that, even if thyroxin is transformed into triiodothyronine before the appearance of its effect on the rate of metabolism, the absence of a response to triiodothyronine in these tissues does not point to their incapacity to deiodinate thyroxin Barac /198/, studying the action of 3, 5, 3'–triiodothyronine on the function of the kidneys of dogs with transplanted kidneys, determined that this derivative increases the venous stream and diuresis in the kidneys, but after a long latent period. Consequently,

triiodothyronine is not the immediately active peripheral form of thyroxin. Upon adding it to tissue sections it has no immediate effect on the absorption of oxygen /572/.

A faster action of triiodothyronine on intact animals and on persons suffering from myxedema may be explained by its faster penetration into the cells and by its weaker bond with proteins. As was shown, the effect of the thyroid hormones is determined not by the total quantity of the hormones in the plasma, but precisely by that part of the hormones which is not bound to the protein.

Thibault's hypothesis that thyroxamine is a derivative having an immediate action, which is responsible for the sensitization of the tissues, was also found to be unsatisfactory. This led the author to search for another derivative, which catalyzes oxidation in the tissues without a latent period. Research in this direction was also made by other scientists Albright and others /181, 582/ upon adding triiodothyronine to in vitro systems containing homogenates or mitochondria of liver or kidneys discovered labeled 3, 5, 3'–triiodothyroacetic acid. Labeled triiodothyroacetic acid was also found in the kidneys and muscles of rats after administering labeled triiodothyronine to intact animals /543, 458/ In relation to the discovery of an acetic acid derivative of iodothyronines, a hypothesis was proposed that this is the active form of the thyroid hormones, having an immediate effect in the cells. The process of the transformation of triiodothyronine into triiodothyroacetic acid may only be a degradation process. But it is not excluded that triiodothyroacetic acid may possess physiological activity at the cellular level. Its physiological effect has been studied in vitro by Thibault and Pitt-Rivers /574, 460/ There are also observations of other authors on the physiological effect of this derivative in in vitro studies. Pitt-Rivers and Thibault reported that the addition of triiodothyro- or tetraiodothyroacetic acid to rat liver sections provoked a sharp increase of the oxygen consumption without a latent period, this does not occur under the action of thyroxin or triiodothyronine The strongest effect of the above derivatives was noted during the first 15 min and then it weakened. The effect of physiological concentrations of the order of 10^{-6} M and less prompted the authors to attibute to the substance a catalytic role also under natural conditions. Higher concentrations have an inhibiting action.

It was shown in experiments on rats with a removed thyroid gland /573/ that the latent period of the thyroxin and triiodothyronine action on the oxygen consumption [illegible]

this is the first proof of the action of thyroxin derivatives without a latent period and that this confirms Thibault's opinion that tri- and tetraiodothyroacetic derivatives of thyroxin are the active forms of the thyroid hormones at the cellular level Thibault emphasized that thyroxin and triiodothyronine show their physiological effects in the tissues only after preliminary transformation into thyroacetic acids

Analogous results were obtained by Donhoffer and others /269, 270, 271/ on thyroidectomized and hypophysectomized rats. Triiodothyroacetic acid provoked immediate augmentation of the oxygen consumption and a rise of body temperature in all hypophysectomized rats, in half of the thyroidectomized rats after intravenous injection and, with one exception, after subcutaneous injection. Triiodothyronine had an immediate effect on almost all hypophysectomized rats after intravenous injection. After subcutaneous injection only 2/3 of the animals showed such a reaction The action of thyroxin was unsteady in hypophysectomized rats, even after intravenous injection

The above results seem absolutely sufficient in order to conclude that triiodothyroacetic acid, in view of its speedy and strong action, is probably the

cellularly active form of the thyroid hormones. But this opinion is far from being generally accepted. A large number of experiments by other researchers could not confirm the results advanced by the supporters of the hypothesis that the acetic acid analogues of thyroxin are the active forms of the hormone. Thus, many in vitro experiments did not succeed in showing an immediate augmentation of the O_2- consumption by liver and kidney sections of hypothyroid rats upon adding triiodothyroacetic and tetraiodothyroacetic acids in concentrations of 10^{-6}—10^{-5} M They augmented consumption in cardiac muscle homogenates, but less than thyroxin. In patients suffering from myxedema the augmentation of basal metabolism, the reduction of cholesterol, and the rise of the PBI level in the blood serum were shown upon administering acetic acid derivatives, but their action, which was qualitatively similar to that of triiodothyronine, is considerably weaker than that of the latter /583, 466/. An analogous result was obtained in experiments on chicks receiving food rich in cholesterol, triiodothyronine and triiodothyroacetic acid have a qualitatively similar action and reduce hypercholesterinemia considerably, but the acetic acid derivative is 10 times weaker than the hormone itself.

Barker /200/ compared the effect of pharmacological doses of thyroxin, triiodothyronine, triiodothyroacetic acid, and tetraiodothyroacetic acid administered to rats four days before beginning the study of the oxygen consumption by tissue section from the killed animals. The comparison of the effect of all the above iodothyronines confirms that, although triiodothyroacetic acid has a certain activity, its metabolic effect is considerably weaker than that of triiodothyronine.

The above results show that the hypothesis accepting triiodothyroacetic acid as the active form of the thyroid hormones at the cellular level is unsound But, in order to draw such a conclusion, it would be necessary to compare the metabolic fate of triiodothyroacetic acid with the transformations of thyroxin and triiodothyronine in the organism after administering them in equal quantities.

As was noted by Larson and Albright /389/, it is probable that the relatively weak effect of exogenously administered triiodothyroacetic acid, observed in humans and animals, could be explained by its not achieving the required concentration inside the cells. In order to check such an opinion, the authors determined the concentrations of triiodothyronine, thyroxin, and triiodothyroacetic acid inside the tissues after administering indicator quantities of these compounds These authors came to the conclusion that, after injection, thyroxin remains basically in the intravascular space, triiodothyronine speedily reaches a relatively high level in the kidneys, liver, heart, and skeletal muscles, triiodothyroacetic acid, though rather speedily cleared from plasma, does not accumulate in the heart, skeletal muscles, or kidney. The relatively slow plasma clearance of triiodothyroacetic acid is probably explained by its slight entry into muscles and kidneys in comparable quantities. A fast removal of the acetic acid derivative by the liver into the intestine occurs in view of its considerable retention in the plasma.

Thus, according to the opinion of Albright and Larson, the relatively weak effect of the exogenously administered triiodothyroacetic acid is explained by the fact that this component does not enter the cells (especially those of the heart, kidneys, and skeletal muscles) to the same extent as triiodothyronine and thyroxin, and that at the same time it is speedily eliminated by the liver. According to their opinion, if triiodothyroacetic acid is an intracellular, metabolically active derivative of the thyroid gland hormones, still the mechanisms of its transport through the cellular membranes cannot be explained.

The above work is a considerable contribution to the solution of the problem of the active forms of the thyroid gland hormones at the cellular level, but it gives no definite answer to this extremely important question, which is related to the

mechanism of the thyroid hormone action. This would necessitate the realization of additional studies, also in vivo, in order to characterize quantitatively the effect of iodothyronines in relation to the quantity of the components penetrating the cells.

Feuer /293/ recently reported the discovery of a new iodinated compound (substance 3) in the composition of the thyroid gland hormones, possessing a direct stimulating effect on respiration and on the accumulation of ester phosphorus during oxidation of succinate and glucose by kidney homogenates. Reports point to the fact that this substance contains bound acetic acid, and acetylation of thyroxin and triiodothyronine by coenzyme A forms the active form of the hormone. These assumptions require testing as well as more convincing proofs.

6 The Mechanism of Action of the Thyroid Hormones

The question of the thyroid hormone mechanism of action, as well as that of hormones in general, and of other biologically active substances, is one of the most interesting, and undoubtedly one of the most important problems of biochemistry If this question may be considered as being satisfactorily answered in regard to water-soluble vitamins, it still remains completely unclear regarding most lipid-soluble vitamins and all the hormones Thus it is not surprising that the attention of a large group of famous scientists has been attracted to the study of the mechanism of action of thyroxin. For the last ten years persistent work has been done in order to throw light on the nature of the intracellular action of the thyroid hormones and on their interaction with cellular structures However, notwithstanding the large number of works, the exact nature of the thyroxin action remains unknown

The extremely varied effect noted after administration of the thyroid hormones caused scientists to believe that there exists an initial action of the hormonal substance on one biochemical point, having a fundamental importance in the cellular metabolism After determining this point it would be possible to explain all the manifestations of the hormonal effect as a consequence of its basic action

As may be seen from the above material, a very large number of enzymes, pertaining to biocatalysts of various biochemical reactions, are influenced by the thyroid gland hormones. In view of the fact that diffuse changes begin after thyroxin reaches concentrations of about 10^{-7} in the body liquids, it seems tempting to assume that the hormone acts as a catalyst for one basic reaction, or that it participates as a coenzyme in the realization of many biochemical reactions. Undoubtedly, the concentration of the hormone at the histological or biochemical point where the action of thyroxin takes place may be many times higher than the diffused concentration inside the cells or in the intracellular fluid But this basic hypothetical reaction in which thyroxin, or any of its active forms, is included, has not yet been determined and this is why it is only possible to express more or less founded suppositions about the mechanism of action of thyroxin.

Several hypotheses have been proposed during the last twenty years on the action of the thyroid hormones at the level of cells and cellular structures, but all have their shortcomings and this is why not one of them is universally accepted. It is possible that the whole action of thyroxin on the oxygen consumption and, indirectly, on the various metabolic processes is explained by its effect on cytochrome [illegible]

enzyme with other enzymes is not determined, it may be accepted that thyroxin has an influence on a series of other enzymes, such as xanthineoxidase, cholinesterase, and lipase

Another hypothesis on the mechanism of action of thyroxin on numerous metabolic processes was expressed by B. I. Gol'dshtein /45/. It is based on facts determined by Gol'dshtein and his co-workers, showing that the administration of thyroid hormones to animals leads to the accumulation of sulfhydryl groups in several tissue and enzymatic proteins. The author who introduced this opinion started from the well-known fact that the activity of some thiolic enzymes in the tissues of animals is augmented after administering thyroid hormones /44/. Taking into account the strengthening effect of thyroxin on a whole series of other enzymes, whose activity is closely tied to the presence of sulfhydryl groups in the proteinic component (papain, cathepsin, carboxylase, lipase, succinic dehydrase, pyruvic oxidase, amino acid dehydrase, adenosine triphosphatase, myokinase), it was assumed that the thyroid gland hormones act on the tissues of the living organism by accumulating SH groups in the tissue proteins and enzymes. This opinion was confirmed by a number of previous studies by the same author and was later reinforced by the results of several new works Thus, the works of Gol'dshtein and his co-workers /46/ showed the augmentation of the quantity and the reacting capacity of the SH groups in tissue proteins under the action of the thyroid gland hormone. A. V. Azyavchik / 4 / separated the protein component of liver d-amino-oxidase and showed the augmentation of the sulfhydryl groups in it under the influence of thyroidine.

According to the opinion of B. I. Gol'dshtein / 46 /, the accumulation of SH groups in tissue proteins and enzymes may occur by way of augmenting the cysteine content as a result of the cystine reduction in the protein molecule, and during augmentation of the total cystine + cysteine content, or by the appearance of homocysteine in the proteins.

A recently published work of B. I. Gol'dshtein / 46 / showed that the content of d-amino-acid oxidase SH groups increased considerably in hyperthyroid rats after acting upon the protein part of the enzyme with hydrogen sulfide. As during this no augmentation of the cysteine + cystine or homocysteine contents was determined in the protein molecule, the author assumes that the increase of the SH group content occurs at the expense of the reduction of the glutathione S-S group, the reactivity of which increases in hyperthyroidism. Furthermore, the author notes that in hyperthyroidism, the SH group content of the proteins is sharply reduced, probably as a result of their oxidation by air oxygen during the secretion process. The augmentation of the oxidation intensity of the SH groups by air oxygen, as well as the reduction of the S-S bonds by hydrogen sulfide in hyperthyroidism, point to the augmentation of the reacting capacity of the SH and S-S protein groups

As a result of such changes in the reacting capacity of the sulfhydryl groups, the reducing systems of the organism, as for example glutathione, transform the S-S groups into SH, and the oxidizing systems on the contrary transform SH into [illegible]

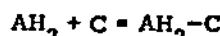
In view of the important role of the sulfhydryl groups for the activity of numerous thiolic enzymes, which have a determining role in the oxidizing-reducing processes, it is undoubtedly very tempting to try to relate the action of the thyroid hormones to their influence on the SH groups But this assumption still does not solve the problem of the biochemical mechanism of thyroxin action, for it is not clear in what manner the molecule of hormonally active substances interacts with the sulfhydryl group, does this process occur directly, or by way of influencing the structure of the protein molecule? Besides this, the hypothesis of the thyroxin action on the metabolic reactions in the cell through increasing the reactivity of the SH groups does not explain the influence of the hormone on a number of very

important enzymes of tissue respiration, as for example on the cytochrome system, which is not related to thiolic enzymes, but without which it is difficult to explain the strengthening of the oxidizing processes observed upon administration of thyroid preparations

A series of new facts which have been determined during the last few years, on the influence of thyroxin on oxidative phosphorylation and on the swelling of mitochondria, are not considered at all by the author of this hypothesis from his point of view In any case, this assumption should be supported by complementary experimental results, *in order to be generally accepted. It should also be noted that* many other factors have an influence on the reactivity of the sulfhydryl groups, from this aspect the action of the thyroid gland hormones is not specific.

In the last decade the generally accepted explanation of the thyroid hormone mechanism of action has been related to the uncoupling of oxidation and phosphorylation. As is known, oxidative phosphorylation is a basic mechanism which helps to transform the respiration energy into energy-rich phosphate bonds. It was thought, up to very recently, that this process takes place in intact mitochondria, but proof has now been obtained that the combination of oxidation with phosphorylation also takes place in mitochondria fragments, obtained by processing them with digitonine /249/, alcohol, and 0.5 M phosphate /621/.

V. P. Skulachov /131/ brings the following diagram on oxidative phosphorylation, proposed by Lehninger:



$$AH_2 + C = AH_2{-}C$$



$$AH_2{-}C + B = A{\sim}C + BH_2$$



$$A{\sim}C + P = A + P{\sim}C$$



$$P{\sim}C + ADP = ATP + C$$



$$AH_2 + B + P + ADP = A + BH_2 + ATP$$

where A and B—neighboring members of the respiratory chain
C—a factor of a supposed protein nature participating in the transesterifications of the combined mechanism.
P—inorganic phosphate

The effectivity of the combined phosphorylation expresses the energetic content of the cell during oxidation of the substrate. It is determined by the ratio of the esterified phophorus content to the oxygen atoms (P:O) A series of com-

tor C to ADP·



$$P{\sim}C + DNP \rightarrow DNP{\sim}C + P$$



$$DNP{\sim}C + H_2O \rightarrow DNP + C$$

Thyroxin also reduces the ratio of esterified phosphorus, i.e., that of energy-rich phosphates to oxygen, but its action appears only when the mitochondria are intact A hypothesis on the action of thyroxin on oxidative phosphorylation was first

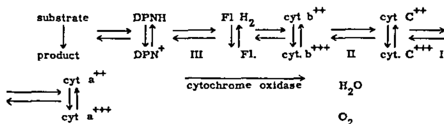
expressed by Marthius and Lardy in 1945 /414, 388/. According to their opinion, the thyroid hormones, just as 2, 4-dinitrophenol, azide, gramicidin, and some other analogous compounds, speed up metabolism, but they lower at the same time its energetic content for work or assimilative processes. They uncouple the oxidation from the phosphorylation processes, which take place simultaneously. The uncoupling action of thyroxin and of compounds which are similar to it is effected, in their opinion, either by the fact that they permit oxidation to take place without phosphorylation, or by way of dephosphorylation of the energy-rich phosphate bonds.

It has been proved by numerous studies that the in vitro addition of thyroxin to tissue preparations or to isolated mitochondria provokes the uncoupling of phosphorylation by the transfer of electrons.

It has been found that such an action is not particular only to thyroxin, but pertains also to all compounds possessing thyroidal activity. Thus, for example, it has been determined that triiodothyronine uncouples phosphorylation from respiration and even suppresses it completely /411/. Nitro- and halophenols, which are similar from the structural point of view, have an analogous action /374/ Thus, oxidative phosphorylation may be considered as being a turning point for the action of thyroxin, in view of the fact that the relation of the tricarboxylic cycle to cell respiration through phosphorylation is still little studied. The specific process of oxidative phosphorylation, occurring through a number of stages at a limited rate, is the basic source for the transformation and accumulation of energy during the metabolic processes.

The reduction of metabolic effectivity, which is ensured by this process, may be considerably more than the compensation of the noneffective energy expenditure by way of augmenting the oxidation rate and, in this manner, will lead to the total expenditure of the energy reserves of the organism.

The sequence of the electron transfer to the mitochondria, where the reaction of phosphorylation is closely combined to respiration, is apparently as follows



[illegible]

ing importance of the inorganic phosphorus concentration and of the phosphate accept which is energy-rich.

In high concentrations dinitrophenol suppresses respiration, possibly because of excess hydrolysis of nucleotides and co-enzymes which are part of the respiratory mechanism. Starting from the action of thyroxin on the elimination of energy-rich phosphate bonds, it is generally accepted today that the noxious and toxic effect

of excess quantities of thyroxin may be, at least to a certain extent, a result of its uncoupling effect.

But there are differences of opinion on the mechanism of the healing action of the thyroid hormones. Is it possible to explain the therapeutic action of small quantities of thyroxin also by its uncoupling effect? In reality, muscular work, which is performed with a smaller expenditure of energy during hypothyroid states than in normal organisms, shows that even a minute quantity of thyroid hormones, which is normally found in the muscles, has an action on the mechanism of energy fixation.

Lardy and his group insist that in physiological concentrations the thyroid hormones may uncouple phosphorylation in only one place of the electron-transporting mechanism and that this may take place exactly until they reach the extent which limits the rate of the constant oxidative phosphorylation state.

Marthius brought results confirming such a hypothesis and Hoch and Lipman /353/ brought proofs of the general uncoupling action of the thyroid hormones. Mitochondria of hyperthyroid animals had half the effectiveness in coupled phosphorylation. According to the extent of ferricyanide reduction and β-oxybutyric acid oxidation, the P·O ratio in normal animals was 2 3 and only 0.68 in hyperthyroid ones.

S.E. Severin /121/, studying oxidative phosphorylation in muscles after denervation and in thyrotoxicosis, could not determine any disorder in the oxidative phosphorylation in these pathological states, but discovered changes in the processes of glycolysis and glycolytic oxidation-reduction This result shows a considerable stability of the combined-mechanism enzymes in pathological states.

The decisive role of enzymes in the action of thyroxin on phosphorylation was later confirmed in experiments on poisoning of enzymes, during which a reduction of the P^{32} cycle, augmented after the action of the thyroid hormones, was observed /322/. Thus, omnipresent energy-rich phosphorus components may control to a certain degree many phases of the metabolism

Thus, it may be generally noted that, except for the above observation of the in vitro effect of thyroxin on oxidative phosphorylation, there was no other in vitro response to thyroxin or thyroglobulin which would be constant and reproducible so that the site of action of the thyroid hormones might be isolated.

Recently, after extensive studies of Lehninger and his co-workers /249/, the initial action of thyroxin on oxidative phosphorylation was doubted. Subsequent authors brought convincing proof of the fact that thyroxin has an initial effect on the membranes of mitochondria, causing the swelling of the particles. Lehninger and his co-workers noted the fact, determined by Marthius and Hess /415/, that thyroxin uncouples oxidative phosphorylation in the liver of rats only after preliminary incubation with mitochondria Some difficulties in reproducing this experiment with mitochondria of rat livers led Hoch and Lipman /353/ to use in their study such effects of mitochondria, isolated from the liver of hamsters, which were found to be probably more permeable to thyroxin.

Lehninger's group determined that the uncoupling of oxidation and phosphorylation is easily obtained also with rat liver mitochondria, but only after the mitochondria have been incubated for a short time in a hypotonic sucrose solution, a method known to bring about changes in the permeability and in the enzymatic organization of mitochondria After such preliminary processing an immediate and considerable and in some cases a total uncoupling was shown in tests on phosphorylation in liver mitochondria. It was further shown in confirmation of the experiments of Ben, as is noted by Emmelot /284/, that magnesium wards off

uncoupling of oxidative phosphorylation by the action of dinitrophenol The analysis of the experimental results, and their comparison with the reports of Aebi and Abelin /177/ about the fact that mitochondria of hyperthyroid tissues are "prone to swelling", led the author to assume that thyroxin acts initially to a certain extent on the mitochondrial structure.

Studying the changes of the dispersion of light by mitochondrial suspensions, Cleland /244/ succeeded in discovering that thyroxin and triiodothyronine provoke speedy swelling of the mitochondria in an isotonic medium. Contrary to this effect of the thyroid hormones dinitrophenol, to which thyroxin is often compared from the aspect of its in vitro action, did not provoke any swelling and was found to be an extremely strong stabilizer /381/. The swelling effect provoked by thyroxin may be demonstrated in physiological concentrations of the hormone, while the effect on phosphorylation appears in concentrations ten times higher than the physiological ones. This effect may be prevented by Mg^{++}, ATP, and dinitrophenol.

Thus, according to the above results it is presumed that there is a basic difference between thyroxin and DNP in regard to their action on mitochondria, although they both uncouple oxidative phosphorylation in a similar manner

Such a basic difference between DNP and thyroxin was clearly and convincingly demonstrated upon studying the dissociation of oxidation and phosphorylation on a multi-enzyme complex, isolated from digitonine extracts of rat liver mitochondria This complex does not possess the highly complex organization of intact mitochondria, but it is probably responsible for the transfer of electrons and for the phosphorylation observed in the mitochondria. Phosphorylation, coupled to the oxidation of β-oxybutyric acid by molecular oxygen, was found to become totally uncoupled by low concentrations of DNP, pentachlorphenol, and gramicidin, in such isolated enzymatic preparations, but was in no case uncoupled by d- or l-thyroxin in concentrations of $5\ 10^{-5}$M, including preliminary incubation with the enzyme, changes of pH, or changes of the Mg concentration

Thus, the action of thyroxin on oxidative phosphorylation demands the presence of intact mitochondria and thyroxin has no uncoupling action on an isolated complex of phosphorylating enzymes. Consequently, the uncoupling of oxidative phosphorylation provoked by thyroxin in the mitochondria does not take place by the interaction of the hormone with the enzymes of the oxidative phosphorylation. These results sooner prompt us to think that the action of thyroxin in vitro is related to the control of a certain structural particularity of the mitochondria or of some other enzymatic function.

In view of the fact that the elimination of energy-rich bonds during oxidation of the substrate is always lower than the quantities calculated theoretically, and in view of the fact that the P O ratio is reduced in the presence of an excess of the oxidation substrate, occuring as a result of a disproportionally increased demand for oxygen, a number of authors have recently been inclined to accept the presence of a second, nonphosphorylating oxidation method in the cells They assume that in the nonphosphorylating method the reactions are directly between the electron carriers. Although the hypothesis of two oxidation methods is as yet insufficiently supported, many experimental facts could be explained satisfactorily with it. According to this concept, the structure of the mitochondria has a decisive role in regulating the relations between the two oxidation methods and this determines the effi...

...nd other sub-

their effect

This is why

their action is revealed only on intact particles and not on their fragments Thus, the uncoupling action of thyroxin on oxidative phosphorylation in intact mitochondria is

not a direct effect and is not a result of direct interaction between the hormones and the enzymes of oxidative phosphorylation.

According to the results of Klemperer /381/, thyroxin is the most effective uncoupling agent. d-thyroxin, dl-thyroxin,and l-diiodotyrosine also have an uncoupling action, but in an identical concentration of 5 10^{-5}M their effect is considerably weaker than that of l-thyroxin; NaI has no action on oxidative phosphorylation.

The addition of magnesium totally removes the action of thyroxin, for it is evidently the antagonist of the hormone in its effect on the structure of the mitochondria. The swelling of isolated mitochondria in the absence of oxidative processes, or of a phosphorylation chain, is also speedily effected by calcium. Several other agents, as for example 2,4-dinitrophenol, dicumarol, pentachlorophenol, uncoupling oxidative phosphorylation, repressed slight spontaneous swellings, which are generally found in mitochondria suspensions /558, 559, 560/. Although there is no cause to relate any in vitro effect of thyroxin on the mitochondria to its physiological action, there are experiments showing that mitochondria isolated from the tissues of hyperthyroid rats swell faster and those from tissues of hypothyroid rats swell more slowly than mitochondria of normal rats.

The opinion of Lehninger and his group, about the fact that thyroxin disorganizes the functional integrity of mitochondria and thus effects its action on oxidative phosphorylation in a specific way, is more and more supported by research made in recent years.

It was revealed in experiments made recently that thyroxin, diethylstilbestrol, and several hepatocarcinogenic substances supress oxidation of glutamic acid by mice liver mitochondria, while there is no such suppression when DPN is present. These results were obtained in experiments in which the oxidative phosphorylation of mitochondria was not disordered. The above studies confirm the opinion that thyroxin acts rather on the biochemical integrity of the mitochondria than on oxidative phosphorylation

Studies made in order to clarify the influence of thyroxin on some DPN-bound dehydrases in mice liver mitochondria showed that,although inhibition of the activity of these dehydrases does not occur in the presence of DPN, it could be concluded that the thyroid hormone liberates a coenzyme from the enzymatically active complex. Ethylenediaminetetracetate, Mg^{++}, and Mn^{++} have an inverse effect, or prevent the liberation of DPN from glutamic acid dehydrases of mitochondria effected by thyroxin.

In a work which has been published very recently, Lehninger, Ray, and Schneider /395/ drew final conclusions from many studies on the influence of thyroxin on the swelling of mitochondria. They determined that thyroxin does not show its effect when DPN is lost from the mitochondria as a result of maintaining them at a temperature of 0°, when the activity of the respiratory chain is not disordered. According to the opinion of these authors, the oxidized state of DPN is the main determining factor of the sensitivity of the mitochondria to thyroxin. Consequently, the bound form of DPN is a target for the thyroxin action.

Thus, studies made during the last years support more and more the conception that the initial action of thyroxin and other analogous compounds is expressed by changes of the biochemical organization of the cellular mitochondria and that uncoupling of oxidative phosphorylation is a consequence of the disorder of this integrity. Such a hypothesis, which has obtained a rather firm experimental support, may explain the various aspects of the action of thyroxin in vivo as well as in vitro. But this hypothesis, even if completely accepted, does not solve the problems of the

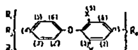
mechanism of action, for we may only say that according to this conception the intact mitochondria are the morphological location of the action of the thyroid hormones, but we cannot point as yet to a relationship between the morphological changes and the biochemical effect at the point of the hormone application. The opinion that there occurs a change of mitochondrial permeability and changes of their enzymatic structure under the influence of thyroxin and triiodothyronine probably *brings us one step nearer to the truth and is by all means a good starting point for* further deeper research.

It is also necessary to pay attention to the circumstance that the problem of the thyroid hormone action is studied in general and is examined here without relation to the nature of the active products at the level of the receptive cells. We have already seen that this problem is by itself complicated enough and the elucidation of the mechanism of action of the thyroid hormones necessarily has to take into account the chemical interaction of this hypothetically active structure with the particular cellular substrate.

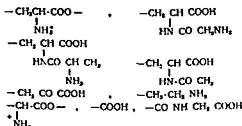
7. The Action of Analogues and of Compounds Related to Thyroxin

The physiological activity of the thyroid gland hormones is related to a characteristic and specific structure, which is found not only in the basic natural thyroid compounds, but is also inherent to a whole series of other artificially obtained substances. Recently a whole series of compounds with some modifications of the thyroxin structure has been synthesized with replacement of iodine by other haloids and groups which had a thyroxin-like action. Consequently, when we speak of the thyroid hormones we do not have in view only thyroxin and triiodothyronine, which have a high degree of biological activity, but also many compounds which are close to thyroxin from the structural point of view. These include halogenated thyronines, isomers of thyroxin,and its analogues and homologues. This is why, when studying structural analogues, evaluation should first be made of what part of the structure is necessary for the physiological activity and what replacements are the most effective in order to obtain a substance with antithyrotoxic activity

Starting from the fact that l-thyroxin may be characterized by its action on various physiological or pathological processes, the evaluation of the biological importance of the various components or groups of its structure is especially interesting. There are reports showing that thyromimetic activity in mammals is a property of compounds having the following general formula /441/

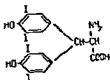


In this formula, R_1 = OH or OCH_3, in the position (4') or (2'), R_2 and R_3 = I, Br, F, or H alone or in combinations, in the positions (3') and (5'), X = I, Br, Cl, and possibly F in the positions (3), (5), and R_4 may be represented by the following groups



The presence of OH in the outer ring in *positions (2') or (4') is necessary for* the activity of thyroxin /441/, the formation of methyl ether with this hydroxyl reduces the activity of thyroxin.

The highly specific nature of the thyroxin core for normal activity was shown as early as 1929 by Harington and McCartney /344/ by the synthesis of isothyroxin, a compound with the same molecular weight and element composition as thyroxin, but absolutely lacking in hormonal activity.



Oxygen in the etheric bond between two phenolic rings may be replaced by a sulfur atom and the thyromimetic effect is conserved to a certain extent, but the diphenyl configuration is determining. The fact that thyroxin-like activity is not completely lost after major changes of the nature of R gives the impression that the critical structure is two haloids in the positions 3, 5 and a hydroxyl or an analogous group in the positions 2', or 4' in the diphenyl ether nucleus. Such a variation suggests that simple compounds must have their own activity, but most of them have only one active group.

The presence of one iodine atom in positions 3 or 3' is a necessary condition for the appearance of activity This activity increases upon substitution in position 5 and is reduced when substitution is made in position 5'. Thus, diiodothyronine is the basis which ensures the optimal initial point for a maximal hormonal activity.

In studies on mammals thyroxin itself constantly exhibits a most complete combination of all properties attributed to the thyroid hormones. But triiodothyro*nine was found to be more active than thyroxin in respect of the augmentation of* oxygen consumption /334/ 3,5-diiodothyropropionic acid was found to be 90% more effective than thyroxin upon studying its action on the metamorphosis of tadpoles

The comparison of the biological activity of a large number of thyroxin analogues and homologues led to the acceptance of two important features determining the effectiveness of the action of the various thyronine derivatives. In the first place come compounds with iodine in the 3, 5, 3' position of the hormone ring, their derivatives are more active than the 3, 5, 3', 5' derivatives of the parahydroxyphenoxyphenol cycle. The second feature is related to the comparison of similar thyronine rings with various changes of the alanine residue. These considerations are of great importance in the evaluation of the hypotheses on the mechanism of action of the thyroid gland hormones.

Nieman /441/ synthesized a large number of tetrahaloid derivatives, containing chlorine, bromine, fluorine, and iodine atoms in positions 3, 5, 3', 5' in various combinations, and determined that they all have a thyroxin-like effect but that not one of them can be compared to thyroxin in regard to the strength of its action. Some nitro derivatives of l-thyronine also have thyroxin-like properties. It was determined, for example, that 3, 5-dinitrothyronine, like thyroxin, inhibits the growth of animals, leads to the suppression of the thyroid gland function, and to the involution of the thymus, but is considerably less active than thyroxin.

Roche and his group /496/, Tomita and Lardy /581/, Bruice, Winzler, Kharasch /232/, Asper, Selenkow, Plamondon,and Wiswell /189, 461, 462, 524/ thoroughly studied the biological activity of iodothyronines and various structural analogues of the thyroid hormones by their effect on the metamorphosis of tadpoles of Rana Temporaria and by their antigoitrogenic action on the enlarged thyroid gland of rats receiving 6-propylthiouracil.

The biological effect of iodothyronines and their structural analogues is compared in Table V, composed according to the results of a number of authors /581, 496/.

As is seen from the table, 3, 5, 3'-iodothyronines exhibit a higher degree of activity than their tetraiodinated homologues, independent of the character of the lateral chain. In a series of iodothyronines, dl-3, 3'—diiodothyronine derivatives have the same activity as thyroxin. It should be noted that the effect on the metamorphosis of tadpoles does not always concur with the capacity of preventing experimental goiter. The action on the development of goiter was found to be extremely high in the derivatives of thyropropionic and thyroacrylic acids and in this relation 3, 5, 3'-triiodothyropropionic acid had an activity 210 times higher than thyroxin A series of nitro-ethers of N-acetyldiiodotyrosine also exhibited weak thyroidal activity in large doses /613/.

Roche and his group also succeeded in showing in a previous work /485/ considerable differences in the efficiency of various iodothyronines in regard to their antigoitrogenic effect. 3, 3'-diiodothyronine has an activity equal to 82% of that of thyroxin, while 3,5-diiodothyronine is completely lacking in antigoitrogenic effect, 3, 3', 5'-triiodothyronine has a very weak activity, only equal to 5% of the activity of thyroxin,and 3, 5, 3'-triiodothyronine, the natural thyroid hormone, has an activity which is 5 to 10 times higher than that of thyroxin. l-triiodothyropropionic acid shows an effect equal to that of thyroxin, and the tetraiodo-derivatives had 75% of the activity of thyroxin

Studies made by Gemmill /318/ on the comparative activity of a series of thyroxin analogues, by way of determining the increase of basal metabolism in thyroidectomized rats upon oral administration of the preparations, gave analogous results Administration of thyroxin, 3, 5, 3'-triiodothyronine, 3, 3'-diiodo-5-bromothyronine provoked an increase of metabolism, while triiodothyronine showed the greater activity in these experiments (augmentation of metabolism by 244%).

According to the results of Barker /200/, triiodothyronine was found to be about four times more active than thyroxin in regard to oxygen consumption and the activity of the thyroxamine was 5 times less. The tetraiodinated analogues with a residue of propionic, acrylic,or acetic acids instead of the alanine had an activity equal to about 75% of that of thyroxin. Tetraiodothyroformic acid had almost no activity and triiodothyroacetic acid had a somewhat stronger activity than thyroxin.

The systematic study of various iodothyronines was performed by Asper, Plamondon, Selenkow, Wiswell /189, 461, 462, 524/. According to the antigoitrogenic effect on rats receiving thiouracil, l-and dl-triiodothyronine were found to be 6 times stronger than thyroxin Results obtained by testing the antigoitrogenic

this effect is as yet generally unclear.

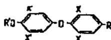
Bruice, Kharasch, Winzler /231/ studied the dependence of the thyroxin-like action on the chemical structure, their studies were based on extensive material

Table V

Relative biological activity of various iodothyronines

NAME	Lateral Chain	Relative activity (on a molar basis)	
		Prevention of goiter	Metamorphosis of tadpoles
dl-thyroxin	$-CH_2-CH-NH_2COOH$	1	1
dl-3, 5, 3'-triiodothyronine	$-CH_2-CH-NH_2COOH$	5	5
d-3, 5, 3'-triiodothyronine	$-CH_2-CH(NH_2)-COOH$	-	3
dl-3, 3', 5'-triiodothyronine	$-CH_2-CH-NH_2COOH$	0.05	0 05
dl-3, 3'-diiodothyronine	$-CH_2-CH-NH_2COOH$	0.82	0
dl-3', 5'-diiodothyronine	$-CH_2-CH-NH_2COOH$	-	0.7
dl-3'-monoiodothyronine	$-CH_2-CH-NH_2COOH$	-	9
Thyroxamine	$-CH_2-CH_2-NH_2$	0.01	36
Triiodothyronamine	$-CH_2-CH_2-NH_2$	0.11	0.1
Diiodothyronamine	$-CH_2-CH_2-NH_2$	0.01	-
Tetraiodothyraniline	$-NH_2$	0.01	0.1
Triiodothyraniline	$-NH_2$	0.01	0.8
Diiodothyraniline	$-NH_2$	0 01	0.1
o-methyldiiodothyraniline	$-NH_2$	0.01	-
3, 5, 3'-triiodothyropyruvic acid	$-CH_2-CO-COOH$	1	1
3, 5, 3', 5'-tetraiodothyropyruvic acid	$-CH_2-CO-COOH$	0.75	0.3
3, 5, 3'-triiodopropionic acid	$-CH_2-CH_2-COOH$	-	290
3, 5, 3', 5'-tetraiodopropionic acid	$-CH_2-CH_2-COOH$	-	120
3, 5, 3'-triiodothyroacrylic acid	$-CH=CH-COOH$	-	65
3, 5, 3', 5'-tetraiodothyroacrylic acid	$-CH=CH-COOH$	-	20
3, 5, 3'-triiodothyrocarbonic acid	$-COOH$	-	1.2
3, 5, 3', 5'-tetraiodothyrocarbonic acid	$-COOH$	-	0.19
3, 5-diiodothyrocarbonic acid	$-COOH$	0	-
3, 5, 3'-trinitrothyronine	$-CH_2-CH-NH_2COOH$	-	0
3, 5, 3', 5'-tetranitrothyronine	$-CH_2-CH-NH_2COOH$	-	0
o-methyltetraiodothyroacrylic acid	$-CH=CH-COOH$	-	3.5
o-methyldiiodothyroacrylic acid	$-CH=CH-COOH$	-	0.6
o-methyl-dl-thyroxin	$CH_2-CH-NH_2COOH$	0.03	1

They studied 47 compounds with the following structure:



where X and X' = I, Br, Cl, F, H, CH_3, NO_2. R' = H, CH_3. R is the ionized group (residue of alanine, acrylic, propionic, acetic acids, $-COOH$, $-NH_2$) The authors came to the conclusion that a thyroxin-like action is related to the electronic character of the diphenyl ether nucleus and depends on the capacity of the X, X' and OR' groups to attract or release electrons. A series of other regularities were also determined, but they were all obtained by empiric methods

According to the results of Bruice, Winzler, Kharasch /231/, who determined the relative activity of 22 thyroxin analogues according to their action on the resorption of the tail of Rana catesbeiana, triiodothyronine was found to be 4 times more active than l-thyroxin and 8 times more active than dl-thyroxin. The substitution of the iodine in positions 3, 5 by methyl groups considerably increases the biological activity of the corresponding iodothyronines. Thus, for example, 3, 5-diiodo-3', 5'-dimethyl-dl-thyronine has 160% of the activity of l-thyroxin, while the l-isomer has 280% of its activity. In tests on tail resorption the propionic acid analogues of thyroxin also exhibited a very high activity.

Tetraiodopropionic acid has an activity 130 times stronger than thyroxin. Its derivative which has no iodine in positions 3', 5' has only 80% of the activity of thyroxin, but was found to be 30 times more active than 3, 5-diiodo-dl-thyronine The presence of an alanine group also increased the activity of the analogue. Upon substituting the iodine atoms in the phenol rings of thyronine by nitro groups compounds are obtained which do not have a typical thyroxin-like action

Bruce /230/ proved the presence of metabolic activity in deaminothyroxin. This component had 30 to 60% of the activity of l-thyroxin.

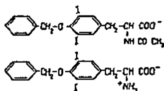
A number of authors made encompassing studies on the physiological activity of d-thyroxin /327/ in regard to its metabolic effect, its action on the level of the plasma PBI and on the absorption of I^{131} by the thyroid gland. It was determined that the clinical effect of d-thyroxin and its action on basal metabolism are only 1/8 to 1/10 of the strength of the l-isomer and 1/5 of the strength in respect to its influence on the PBI. The effect of d-thyroxin on basal metabolism was particularly weak and was only 1/25 as strong as that of l-thyroxin. As to its action on the absorption of I^{131}, the d-isomer has 50% of the activity of the l-isomer and consequently d-thyroxin could in a number of cases suppress the thyrotropic activity of the pituitary, without any considerable influence on the rate of metabolism.

Frieden and others /313/ determined the presence of a thyroxin-like action *in the following substituted phenols containing iodine: 3,5-diiodo-4-hydroxy derivatives* of benzoin, phenylacetic and phenylpropionic acids, and diiodotyrosine. The activity of fresh solutions could be inhibited by thiouracil, 2-mercaptoimidazole. But the addition of the above goitrogenic agents to standing solutions had no inhibiting influence on the thyroidal activity of diiodotyrosine. The authors explained such an effect by the condensation of the phenyl substitutions in preparation which have stood for a long time, with formation of biologically active compounds. They showed the reaction of condensation in model experiments with the formation of diphenyl ethers of acetic and propionic acid derivatives. This process is inhibited by goitrogenic factors, but they cannot suppress the action of the biologically active component which is already formed.

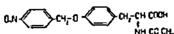
Tests of the biological action of the various analogues and homologues of thyroxin showed that some positions of the haloid in the thyronine ring form non-active compounds. It has been determined that the presence of the haloid in positions 2, 6 leads to the formation of products which are inert from the biological aspect. There is a series of compounds related to thyroxin by their structure, but having an antagonistic effect in regard to the thyroid hormones.

Wolley /34, 613/ was the first to note the possibility of suppressing the action of thyroxin by compounds which have a similar structure. The author tested the particularities of a series of thyroxin and diiodotyrosine analogues and showed that some ethers of N-acetyl-3, 5-diiodo-l-tyrosine have an antagonistic effect in regard to thyroxin when tested on tadpoles. N-acetyl-3, 5-diiodo-l-tyrosine and N-acetyl-o-methyl-dl-thyroxin had no such effect.

Frieden and Winzler /314/ confirmed the inhibiting effect of N-acetyl-3, 5-diiodo-l-tyrosine and brought proofs according to which the antagonism of thyroxin and of the structurally related compounds may be a competitive process. According to the results of Frieden and Winzler, benzyl ether of 3, 5-diiodo-l-tyrosine is a more effective antagonist of thyroxin while acting on tadpoles than N-acetyl derivatives.



Wolley synthesized a series of thyroxin derivatives by substituting the second phenyl ring of thyronine with paranitrobenzene, paranitrophenylethyl, or even benzyl and butyl radicals. They all showed an antagonistic action in relation to thyroxin, reducing the rate of tadpole metamorphosis provoked by thyroxin.



Analogues of thyroxin obtained by shortening the lateral chain by substitution of the alanine residue by glycine had no antagonistic effect.

Most thyroxin antagonists contain iodine in positions 2, 6, counting from the oxygen bond /231/. 2, 6-diiodothyronine also has an inhibiting action on thyroxin. Alkyl ethers of 3,5-diiodo-4-hydroxybenzoic acid, as well as its monoiodo derivatives, form a series of strong antithyroid agents /608/. Hydroxylation of the alkyl group augments the antithyroid activity of the lower ethers. The most simple and reliable antithyroid substances were found to be those containing mainly the diiodophenoxy group /407, 609/.

There are some reports showing that butylic ether of 3,5-diiodo-4-hydroxybenzoic acid and its analogues block the transformation of thyroxin into triiodothyronine. It is important to note that these analogues increase the physiological activity of triiodothyronine and reduce its liberation Van Arsdell and Williams /589/ showed that these compounds reduce the rate of thyroxin and of triiodothyronine destruction in the organism; a reduction of the binding of thyroxin to the albumins of the

serum also takes place at the same time.

The study of the antithyroxin activity of the thyroxin analogues performed by Cortell /250/ showed that thyronine and 3'-fluorothyronine have no thyromimetic or antagonistic action. The antagonistic action of tyrosine derivatives was also studied. Diiodotyrosine was found to be effective in regard to the reduction of the metabolic rate of patients suffering from toxic goiter. But there are indications that its action is not greater than that contained in its iodine molecule and is very similar to the antithyroxin effect of iodine. The following question is not completely clear: does diiodotyrosine have a thyromimetic activity or is it completely lacking in such a property? Opinions have been expressed that diiodotyrosine, inactive in humans, may be found to be effective on lower animals.

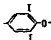
Vind, Kharasch, and Stowell /597/ studied a series of thyroxin and diiodotyrosine analogues from the aspects of the antagonistic action and the antithyroid effect, and they became convinced that pure diiodothyronine does not have a thyromimetic activity. They showed that a series of its sulfur-containing analogues have an antagonistic effect in relation to thyroxin.

Tyrosine dibromide and diiodotyrosine also suppress various manifestations of thyroid activity, but there are still several controversial points to this effect. 3-fluorotyrosine and 3-fluoro-4-hydroxy-phenylacetic acid were also studied in relation to their antagonistic action on thyroxin. This last compound had a noncompetitive influence on the hormone.

The metabolic reaction of rats to thyroxin or to other thyroid preparations is reduced by methylthiouracil and those which have become hypothyroid under the action of thiouracil are less sensitive to thyroxin. But these studies do not give any basis to come to conclusions about the existence of structural interrelations between the thyroid hormones and these preparations. The action of such thyrostatic substances may rather be a toxic effect of the thiouracil derivatives than an antagonism to thyroxin.

Other agents exhibiting an antagonistic effect possibly are real thyroxin antagonists. The antithyroid activity of cholesterol or carotene has probably no structural relation to it. Although vitamins may remove the toxic effect of administered thyroid hormones, their protecting action probably basically reflects the overcoming of a relative vitamin insufficiency /277/.

On the basis of existing results it is possible to conclude in general that the configuration



exhibits antithyroid activity based on structural analogies, with wide possibilities of variation effected by substituting each of the above free valencies by various groups.

Chapter VI

THE HORMONES OF THE THYROID GLAND IN VARIOUS PHYSIOLOGICAL STATES

(gormony shchitovidnoi zhelezy pri nekotorykh fiziologicheskikh sostoyaniyakh)

The function of the thyroid gland is subjected to fluctuations during ontogeny and some physiological states. Changes of the thyroid gland function are reflected in the fluctuations of the radioiodine absorption, in changes of the blood PBI content, and in other indicators.

Many studies have been made on the changes of the thyroid gland function depending on the age of the subject. Martmer et al. /416/ compared the absorption of radio iodine by the thyroid gland of premature children and came to the conclusion that the activity of their thyroid gland does not differ from that of healthy children. A somewhat augmented activity of thyroid gland function, especially at an early age, was determined by other studies made on children. The work of Oliner et al /445/ notes that in children under the age of 18 the absorption values are from 17 to 50%, and the average is 31% of the administered dose. In children under the age of 4 years the PBI content of the blood was also increased. Tangheroni et al. /564/, studying the function of the thyroid gland in children during the first year of life, obtained similar results. They discovered that 12 hours after administering radioiodine the absorption of the thyroid gland of nursing babies averaged 70% of the administered dose. Conversion was also considerably increased and was equal to 38% after 12 hours. Consequently, the relative hyperactivity of the thyroid gland in early age, as compared to adults, is acceptable.

Sheline, Koulischer, and Pickering /529/, studying the absorption of radioiodine by the thyroid gland in euthyroid, hypothyroid, and hyperthyroid children under the age of 18 years, could not determine any correspondence between age and the extent of absorption in older children. It is generally accepted that after the age of 10 it is not possible any more to note any differences between the activity of the thyroid glands of children and adults.

There is a considerable number of works on the activity of the thyroid gland in advanced old age, but controversial opinions are expressed on this question. There is a widespread opinion, based on the study of basal metabolism, that in advanced old age, due to degenerative changes in the gland, hypofunction sets in and the metabolism and the oxygen consumption are reduced But the most recent results obtained by studying the metabolic rate by tests with radioiodine and by the index $= \frac{\text{protein bound I} \times 100}{\text{total I}}$ in aged persons, show the transformation rate of inorganic iodine into an organic form, the augmentation of the thyroid gland secretion without thyroxinemia, and also hyperfunction of the thyroid gland without changes of the basal metabolism. On the basis of their studies Scazziga, Barbieri and Beraud /516/ expressed the opinion that hyperfunction of the gland in old people is a proof of the disorder of the thyroxin action on the peripheral tissues. Thus,

augmented secretion of the thyroid hormones is an expression of the compensating metabolic process in advanced age, when senile involution of the tissue leads to a decrease of the oxidative processes in the cells.

There are also other works pointing to the reduction of thyroid gland function in aged persons. Thus, for example, Parchon, Aslan, and Bojinescu /451/ determined the function of the thyroid gland in old people by the I^{131}-binding and by the dynamics of the hormonal iodine. According to the results of these authors, the binding of iodine in advanced old age is reduced in the same manner as is noted in hypothyroidism and the quantity of the hormones and their secretion into the blood correspond to cases of hyperthyroidism.

Verzar and Freyberg /594/ compared the activity of the thyroid gland of old rats, aged 20 to 29 months, to the activity of young ones, aged 7 to 9 months. It was determined that in old rats the iodine secretion of the thyroid gland is slowed down; excretion of I^{131} in urine is also reduced.

Contradicting results are probably due to deficiencies in the technique of determination and to different methods of research. Additional study, with the use of other criteria for evaluating the functional state of the gland, is evidently needed in order to solve this question definitely.

In healthy adults considerable variations in the I^{131} absorption during 24 hours are also noted. Pochin /463/ discovered such variations upon studying the functional state of the thyroid gland during the menstrual cycle and pregnancy.

Hare and Haigh /343/ also determined variations in the I^{131} uptake by healthy subjects during 24 hours.

When the I^{132} isotope of iodine, which has a halflife of 2 26 hours, became available and it was possible to reduce the indicator dose during the study of the functional state of the thyroid gland, it was found very convenient for use in such studies on healthy persons. The irradiation dose of the thyroid glands is considerably reduced when using this isotope and it is possible to perform repeated studies on the same person after short time intervals.

Halnan and Pochin /338/, using I^{132}, studied the possibility of repeating the absorption test on 5 patients daily and discovered considerable unexpected variations of the radioiodine absorption per hour.

Fellinger, Hoefer, and Vetter /291/ also found considerable differences in the iodine absorption of the thyroid glands of several patients in 24 hours and the authors attribute this to fluctuations of the iodine content in the food.

François, Goldberg et al. /309/ studied the radioiodine uptake in the neck region and its excretion in urine of healthy men by using I^{131} and revealed the presence of physiological fluctuations of the absorption, during 6 hours, of up to 14.4 %, and fluctuations of urinary excretion from 6 to 9 %.

All the above results point to the presence of small but constant fluctuations in the functional state of the thyroid gland, but the causes of these variations have not been studied in detail.

More considerable changes of the function of the thyroid gland are observed during pregnancy. The macroscopic growth of the thyroid gland during pregnancy has been known for a long time; histological changes were later also determined. Before the beginning of the use of the radioiodine isotope for studying the functional state of the thyroid gland, there were not enough specific tests in order

to evaluate quantitatively small fluctuations of the thyroid hormone content in the blood and tissues. This is why the determination of the changes of the thyroid gland function during pregnancy were limited to the study of basal metabolism. It was determined that in the second half of pregnancy basal metabolism increases by 10 to 50% in 50% of the cases and by 10% in the rest.

The augmentation of the I^{131} uptake during pregnancy has been shown in a number of studies /337/. It is reduced after birth, dropping sometimes below the normal values. On the basis of the study made on 40 pregnant women, L.I. Lobanovskaya et al./90/ came to the conclusion that the augmentation of the size and the increase of the function of the thyroid gland are more intensive during the second half of pregnancy than during the first months, no symptoms of thyrotoxicosis are noted during this time.

A number of authors determined that the quantity of PBI increases during pregnancy. The increase starts during the first months after conception and then remains without any basic change at a level of 6.2-11.12 μg%. Results published on the changes of the PBI content and of thyroxin in the blood during pregnancy were summarized in the report by Pitt-Rivers /457/. As is noted in this report, notwithstanding the lack of changes of basal metabolism up to 7 months, PBI is augmented due to an increase of the thyroxin content of the blood .

Ferrare and Skort (cit. from Pitt Rivers,/457/) showed the augmentation of thyroxin in the plasma by chromatographic analysis. But, according to their assumption, the mother does not use thyroxin in a normal manner during pregnancy, or she possibly possesses defence mechanisms against thyroxin, due to which manifestations of thyrotoxicosis do not set in. The administration of triiodothyronine reduces the physiologically increased level of PBI in pregnant women As was noted by Werner /603/, the interrelation pituitary–thyroid gland is not changed in pregnant women and the increase in the content of proteinic iodine is not provoked by a disorder of this interrelation, as occurs in hyperthyroidism.

Dowling et al./274/ point out that the capacity of the blood proteins to bind thyroxin increases during pregnancy. According to the opinion of these authors, such a change of the thyroxin-binding capacity of the plasma is a compensative mechanism and is directly related to the increase of esterogen content during pregnancy.

An increase of the PBI level of the blood was also discovered in newborn children. According to the opinion of Dowling and others, this points to an increase in the binding of thyroxin

Robbins and Nelson /475/ studied the thyroxin-binding capacity of serum α-globulin of pregnant women and newborn children by way of incubating the serum with I^{131}-labeled thyroxin. The authors observed that this capacity of the serum of pregnant women is 2.5 times higher than that of nonpregnant ones, and in newborn children it is 1.5 times higher than in adults, but lower than that of the mother. The above facts may serve to confirm the existing opinion of the possible passage of the thyroid hormones through the placenta. Although this question has not been definitely answered as yet, a series of convincing experiments on animals and observations on persons already exist, showing the permeability of the placenta to hormones of the thyroid glands. Thus, for example, S.I. Tereza /138/ determined on rabbits, as early as 1940, that the hormones of the thyroid gland pass from the mother to the fetus and that this is one of the factors stimulating the growth of the latter and [illegible] gland. Grumbach and Werner (cit. from [illegible] regnant women 10 to 169 [illegible] proteins in the fetus at [illegible] oxin and birth. In ac-

The production by embryos of thyroxin, which also enters the blood during the last months of pregnancy, has been shown by experiments on pregnant rats. As is noted by M.G. Zaks /59/, athyroidism does not prevent conception, but the fertilized cell speedily dies. This fact also points to an indispensable need in thyroid hormone during differentiation of the embryo, beginning from the first days of life.

It has recently been shown that 3,3'-diiodo-1-thyronine speedily enters the blood of the fetus after an intravenous injection to the pregnant rat of compounds labelled in position 3'; inverse passage from the fetus to the mother was difficult.

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the higher sections of the central nervous system with caffein it was also possible to observe the disappearance of the thyrotropic function in mice.

Sectioning of the mesencephalon /185/, of the stem, of the pituitary, and lesions of the hypothalamus /553/ provoke the cessation of the thyrotropic hormone secretion and thus lead to the suppression of the thyroid gland function.

Close interactions between the diencephalon and the hypothalamic-pituitary system in the regulation of the metabolic processes have been postulated during the last years; the role of the hypothalamus in the regulation of the pituitary function has been particularly emphasized. Thus, the influence of the higher sections of the central nervous system on the function of the thyroid gland is effected through the control of the thyrotropic nuclei of the hypothalamic region.

But B.V. Aleshin /10/ proved that the influence of the central nervous system on the thyroid gland may by-pass the hypophysis cerebri. B.V. Aleshin and N.S. Demidenko /12/ point to experiments with implantation of discs on the surface of the brain, which led to the weakening of the thyroid gland function. Experimental neurosis, provoking a sharp disorganization in the central nervous system, also led to manifestations of hypofunction. Morphological changes characteristic of a reduced function of the thyroid gland during these states were shown in the histological studies of V.I. Arkhipenko /14/. According to the results of these authors, lack of parallelism between the activity of the thyroid gland and the functional state of the pituitary is observed during disorders of the brain activity. B.V. Aleshin and N.S. Demidenko /11/ deduct from this that the impulses pass from the brain to the gland without participation of the pituitary, i.e., in a parahypophyseal manner, through the parasympathetic neural stems. They support this deduction with experiments in which they show the increase of cholinergic substances in the thyroid gland upon applying tampons to the retrospinal zone.

The same proof is brought in the work of R.D. Vyazovskaya and I.B. Simon /36/. They also determined an increase of the quantity of cholinergic substances in the tissue of a gland removed because of exophtalmic thyrotoxicosis.

But the existence of parahypophyseal transmission lines of the cortical influences on the thyroid gland is not generally accepted.

Experimental studies exist, demonstrating entirely opposed results M.G. Amiragova /13/ showed the realization of cortical influences on the secretory activity of the thyroid gland through the pituitary as well as through the adrenal glands. She rejects the possibility of direct transmission of the cortical impulses on the secretory function of the thyroid gland through the neural conductors. This is proved by the impossibility of transmitting impulses of the brain cortex after removal of the pituitary, of one adrenal gland, and sectioning of n. splanchnici.

The question of the role of the sympathetic and parasympathetic nervous system in the regulation of the thyroid gland function has not been definitely solved. It is known that the thyroid gland contains many fibers formed by the terminal plexus of the sympathetic nerve. The appearance of morphological changes of the intraorganic nerves during pathological states of the thyroid gland was shown in the works of E.I. Tarakanov /137/. Early works of Kennon and others (cit. from Trendelenburg, /142/), and new results obtained by A.V. Tonkikh /139/ show that chronic stimulation of the sympathetic nerve provokes manifestations of hyperthyroidism.

Other works by Russian scientists point to the fact that the autonomic nervous system influences the morphology and the function of the thyroid gland. Some authors also noted some manifestations of thyroid gland stimulation during

Chapter VII

THE REGULATION OF THE FUNCTION OF THE THYROID GLAND

(regulyatsiya funktsii shchitovidnoi zhelezy)

1. The Neural Regulation of the Function of the Thyroid Gland

The attention of a large number of researchers has been attracted for a long time to questions of the regulation of the thyroid gland function. These problems have developed intensively during the last years. The control of the brain hemispheres on the function of the thyroid gland was shown in a series of experiments with conditioned-reflex regulation of the gland activity. The influence of the central nervous system on the function of the gland is particularly clearly expressed in pathological states. The pituitary-hypothalamic system has an important role in the transmission of the influence of the central nervous system to the thyroid gland. Its role has been convincingly shown in experiments by sectioning the neural stem in various places and stimulating various regions of the diencephalon.

The well-known work of R.P. Ol'nyanskaya /108/ threw light on the participation of the thyroid gland in the unconditioned and conditioned-reflex regulation of gaseous metabolism. She obtained a conditioned-reflex increase of basal metabolism in a dog upon combining the administration of thyroxin to the action of an indifferent stimulator, when the thyroid gland was devoid of innervation.

M.S. Kokhana /86/, provoking repeated defensive reactions in rabbits, obtained a hyperfunction of the thyroid gland. In rabbits in which the nervous centers of the posterior part of the hypothalamus were affected no hyperfunction of the thyroid gland was observed during the elaboration of defensive reactions.

I.A. Eskin and Yu. B. Skebel'skaya /175/ provoked hyperfunction of the thyroid gland by increasing the stimulation processes in the brain by administering caffein and phenamine.

E.A. Kolli /81/ studied the absorption of radioiodine by the thyroid gland and the formation of a fraction of organically bound iodine by the action of pharmacological substances stimulating the central nervous system and determined the increase of both these indicators under the action of thyroxin.

Yu. B. Skebel'skaya /127/ elaborated a conditioned reflex to the increase and the reduction of the pituitary function in rats, by way of administering thyroxin, methylthiouracil, and thyroidine, and showed that the thyrotropic function of the pituitary and the thyroid gland activity which is related to it are controlled by the cortex of the brain.

Analogous results were obtained by P.A. Vunder /35/, who provoked in rats a conditioned-reflex reaction of the thyroid gland to the thyroid hormone, which was then replaced by a physiological solution. Upon increasing the stimulation of

capturing capacity of intact rats falls to 1/3 of its normal value after hypophysectomy and the rate of secretion of the labeled hormone by the thyroid gland is reduced during the first five days after removal of the pituitary.

It was also found that, althougn the thyroid gland of hypophysectomized rats concentrates a considerably smaller quantity of iodine, it retains the capacity of transforming it into an organic form, but this process takes place considerably more slowly. According to the results of Morton et al. /429/, the greatest part of the iodine captured by the thyroid gland is found in it in the form of diiodotyrosine. The process of diiodotyrosine formation takes place easily in hypophysectomized rats, but the transformation of diiodotyrosine into thyroxin is found to be considerably disordered. According to the opinion of the above authors, the condensation of iodotyrosine molecules is under the special control of the thyrotropic hormone of the pituitary. This is why the ratio of thyroxin to the diiodotyrosine fraction is reduced in hypophysectomized animals, as compared to the thyroid gland of intact rats.

The thyrotropic function of the pituitary is controlled by the nervous system and the hypothalamus has a special position in this control. It has been shown in a series of studies that a hypothalamic neurohumoral factor may be applied to the anterior lobe of the pituitary and it has an influence on its activity /533/.

As is noted by A. V. Tonkikh /141/, there is a neural bond between the anterior lobe of the pituitary and the hypothalamus, through the stalk of the pituitary, but this bond is not direct and passes through the posterior lobe of the pituitary. Sectioning of the diencephalon reduces the secretion of the thyroid hormone and thus reduces the secretion of I^{131} from the thyroid gland. But the secretion of the thyroid gland returned to its normal level twelve days after disruption of the bond with the mesencephalon /185/. The study of the distribution and the metabolism of iodine in the brain by means of radioiodine also confirms the existence of close interrelations between the diencephalon and the thyroid gland.

The thyrotropic hormone is not considered at present as being a homogeneous substance. Three active principles may be discerned in it : a factor provoking exophthalmos, a growth factor, and a metabolic factor /553/. The growth factor, provoking growth of the thyroid gland follicles, was called thyroproliferin and the metabolic factor, stimulating the chemical synthesis and the secrection of hormone, was called thyrosecretin. These three factors are directed in various ways by the hypothalamus.

Strictly speaking, the opinion on the existence of several factors in TSH arose upon analyzing the results of the study of various thyroid gland parameters after disruption of the bond between the pituitary and the hypothalamus It was found that if the bond between the pituitary and the hypothalamus is ruptured growth of the thyroid gland is reduced, but the function of concentrating iodine remains unchanged. This led to the conclusion that there exist a separate growth hormone and a metabolic hormone in TSH.

It has recently been possible to separate the exophthalmic factor from the thyrotropic hormone by way of chemical fractionation. It was also discovered by Dobyns and Wilson /268/ in the serum of patients suffering from progressive exophthalmos.

The study of the metabolism of the thyrotropic hormone gives reason to assume that the thyroid gland itself [illegible]

is considerably increased in hyperthyroidism*.

* [Sic, apparently hypothyroidism is meant].

stimulation of the sympathetic nervous system by administration of adrenalin. But such results could not be confirmed by other researchers. This is why N.B. Medvedeva /96/ was probably right when she called for caution in concluding that the sympathetic nerve is the secretory nerve of the thyroid gland.

Some authors affirm that the nervous system controls the activity of the thyroid gland in an indirect manner, by influencing its blood circulation.

Thus, the question of the transmission of the cortical impulses to the thyroid gland through the neural tracts and also the role of the sympathetic nervous system in regulating the hormonal function of the gland are not yet fully clear.

2. *The Role of the Anterior Lobe of the Pituitary in the Thyroid Function*

At the present state of our knowledge, the direct regulation by the anterior lobe of the pituitary of the gland activity, from the absorption of iodine to the secretion of the thyroid hormones, is an indisputable fact. The hypophysis cerebri, producing a special thyrotropic hormone, constantly controls the functions of the thyroid gland.

The extensive publications on the question of the interrelations of the pituitary and the thyroid gland will not be examined here and we will only examine the results obtained in *recent research*.

The pituitary controls the function of the thyroid gland by excreting into the blood stream a thyrotropic (thyroid stimulating) hormone (TSH). This hormone was recently obtained in a highly purified form by Stilmen and his co-workers (cit. from the book Belki (The Proteins), /18/) after many efforts.

Under the action of this hormone the cells of the thyroid gland swell considerably and take on a cylindrical shape, the intrafollicular colloid becomes diluted and is resorbed by the cells and secreted into the blood or lymph channel. It has been determined in humans that upon administering thyrotropic hormone its action is clearly proved by the loss of the thyroid gland hormone. During this time the PBI of the blood increases and the radioiodine in the thyroid gland is reduced Such an effect is considered as being the result of the activation of the proteolytic enzyme of the gland by the thyrotropic hormone.

Thus, the initial action of the thyrotropic hormone is the separation of thyroxin from the intrafollicular thyroglobulin. The growth of the thyroid gland cells and the increase of its iodine-concentrating function take place as a consequence of [illegible] The stimulated thyroid [illegible] -otro- [illegible] -part of the *absorbed radioiodine is transformed into* thyroxin.

Hypophysectomy has an inverse effect; it leads to the suppression of the thyroid gland function, which is reflected in the various stages of hormone formation. A sharp reduction of the iodine capture by the thyroid gland is noted in hypophysectomized animals /453/. According to the results of Van der Laan and Greer (cit. from *The Hormones, /358/) the iodine capture by the thyroid gland* reached only 10% of its normal value after hypophysectomy.

It was also reported in this study that hypophysectomized animals exhibit a weakened function of iodine binding and that this capacity returns upon administering thyrotropic hormone. According to the opinion of some authors, the iodine

The possibility of obtaining S^{35}-labeled TSH permitted Sonnenberg and Money /534/ to study the distribution of activity after intravenous administration of the thyroid stimulating hormone. It was found that upon administering large doses of the hormone, more of it is accumulated in the liver and kidneys than in the thyroid gland, although strong activity is found in the latter. But, upon administering small quantities of the hormone, the S^{35}-labeled preparations are accumulated more in the thyroid gland.

There is also proof of the chemical inactivation of the thyrotropic hormone in the peripheral blood by thyroxin. It was postulated that a normal thyroid gland changes the thyrotropic hormone, and that in Basedow's disease the thyroid gland inactivates even greater quantities of this pituitary hormone.

The capacity of the thyroid gland to inactivate the thyrotropic hormone was also studied on tissue cultures by Rawson, Sterne, and Aub (cit from The Hormones /358/). It was shown that an explant of the thyroid gland of a rabbit inactivates twelve units of TSH, whereas explants of a thymus gland or a lymph node, which also become larger in Basedow's disease, were able to inactivate only six units of TSH. An explant obtained from a patient with Basedow's disease inactivated almost twice as much TSH as a normal gland, while a gland in which the colloid was changed did not inactivate the thyrotropic hormone at all In another work, the same authors point to the fact that TSH inactivated by the thyroid gland may be reactivated by the action of some restoring agents, as for example thiouracil or 5-amino-thiazol-thiol. This leads to the conclusion that during an increase of the pituitary activity, the thyrotropic hormone is inactivated by some enzymatic oxidizing systems Studies of D'Angelo /254/ showed a very slow disappearance of exogenous TSH in hypophysectomized rats. This may be accelerated with thyroxin and triiodothyronine. According to the author's opinion, a stable level of TSH in hyperplastic and aplastic states of the thyroid gland, is not in accord with the fact that the thyroid gland has a basic role in the metabolism of this hormone. The disappearance of TSH from the blood depends mainly on the rate of metabolism.

3. The Interrelations of the Thyroid Gland with Other Glands of Internal Secretion

Notwithstanding the exceptional situation of the pituitary in the regulation of the thyroid gland function, other glands of internal secretion also influence its activity. The growth hormone and ACTH, which probably intervene in the peripheral action of the thyroid hormones, have a considerable influence on the function of the thyroid gland.

It has recently been shown by Evans et al. /286/ that the growth hormone increases calorigenesis in hypophysectomized rats. This action is probably effected by way of increasing the function of the thyroid gland, and this is seen morphologically and functionally. The growth hormone also increases the calorigenic action of thyroxin in hypophysectomized rats, and this is shown by the increase of thermo- [illegible] er- [illegible] 'TH, [illegible] steroids. ACTH and glucocorticoids of the adrenal glands have a calorigenic effect on hypophysectomized and thyroidectomized animals. Many authors affirm that more than one factor acting on the thyroid gland is found in the anterior lobe of the pituitary. In his studies, Beck /207/ showed the increase of I^{131} liberation from the thyroid gland under the action of [illegible]

A report by Adams /176/ has recently appeared on his discovery of atypical TSH in pituitary extracts and in the serum of *some patients suffering* from thyrotoxicosis; this TSH, upon being administered to guinea pigs which had received I^{131}-thyroxin, prolonged the period of I^{131} secretion from the thyroid gland and the period of the augmentation of its concentration in the *plasma. The author* accepts the identity of this hormone with the exophthalmic factor of Dobyns and Wilson.

The maximum quantity of thyrotropic hormone was found in the blood of people suffering from myxedema. Results obtained confirm the opinion that an increased *level of the thyroid* hormones in the blood suppresses the thyrotropic function of the pituitary. Besides this, it is accepted that the pituitary of totally thyroidectomized patients produces greater quantities of thyrotropic hormones, in view of the functional hypertrophy of its anterior lobe.

Thus, the thyroid hormones and the thyrotropic hormone are in a state of reciprocal stimulation and inhibition. Increase of the thyrotropic hormone augments the production of the thyroid hormones and, inversely, an increase of the thyroid hormone concentration in the blood reduces the secretion of the thyrotropic hormone. This mechanism serves to maintain a constant level of thyroid gland hormones in the blood /283/.

The methods of the thyroid hormone action on the anterior lobe of the pituitary are the subject of lengthy discussions. Does the thyroid hormone effect the anterior lobe of the pituitary directly, or through the hypothalamic structure? Recent studies of Holmgren /356/ clearly showed that a receptor, sensitive to thyroid gland hormones, is disposed in the anterior lobe of the pituitary itself. The hormones of the thyroid gland suppress the function of the gland, due to a depressing action on the pituitary function. All the aspects of the interrelations inside the cortex-hypothalamus-pituitary-thyroid gland system can be represented by a diagram (Figure 4).

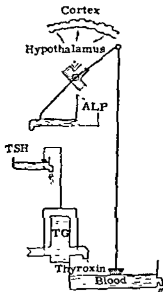


FIGURE 4. Schematic Representation of the Regulating Role of the Level of Thyroxin in the Blood

A large dose of the thyrotropic hormone swiftly disappears from the blood; only three percent of the intravenously administered thyrotropic hormone remains in the plasma after one hour. It is not clear where its total inactivation takes place.

gland under the action of the steroid hormones. There are several results on the mechanism of ACTH and cortisone action on the metabolism of iodine, showing that they suppress the secretion of the thyrotropic hormone from the gland. In hypophysectomized rats and rabbits ACTH does not provoke a reduction of the rate of iodine secretion by the gland, which has already been suppressed, but inhibits the secretion of radioiodine from the gland in response to exogenous TSH /128/. Results obtained in Brown-Grant's laboratory also confirm the hypothesis that ACTH and cortisone reduce the function of the thyroid gland by suppressing the secretion of the thyrotropic hormone. After administration of cortisone Halmi and Barker /339/ determined morphological changes of the thyroid gland cells, characteristic of its augmented activity. Consequently, the reduction of the thyroid gland activity after administration of cortisone, which is noted by many authors, is not provoked by the suppression of the TSH production but by other factors. During the action of cortisone such factors may be: changes of the extrathyroidal iodine metabolism, suppression of I^{131} absorption by the thyroid gland, or real antithyroid (thiouracil-like) activity.

The latter explanation concurs with Skebel'skaya's opinion. It follows from the experimental results of Yu. B. Skebel'skaya /128/ and of I.A. Eskin and Yu. B. Skebel'skaya /174/ that the action of ACTH on the thyroid gland takes place in two phases: the thyrotropic hormones first become reduced in the pituitary and then the reactivity of the thyroid gland to the thyrotropic hormone is weakened. In her next work Skebel'skaya /129/ showed that ACTH also exhibits its action after removal of the adrenal glands. Consequently, ACTH may have a direct action on the tissue of the thyroid gland, without participation of the adrenal cortex. The author concludes from this that the adrenal cortex has no perceptible role in the reaction of the thyroid gland to exogenous or endogenous ACTH.

Gannong and Hildegard /317/ also could not note any considerable reduction of the I^{131}-absorption by the thyroid gland of normal rats during repeated traumas, i.e., during a state of stress which strengthens the function of the adrenal cortex

Mikulaj and Nemeth /420/ and B.Z. Gincherman /42/ studied the function of the adrenal cortex in patients suffering from thyrotoxicosis. According to their results, a reduction of the secretory function of the adrenal cortex is noted during thyrotoxicosis. According to the results of B.Z. Gincherman, hypofunction of the cortex of the adrenal glands is discovered by the reduction of the urea-chlorine-water index and, according to the studies of Mikulaj and others, this is explained by the exhaustion of the functional capacity.

Jakobson /366/ discovered in patients suffering from thyrotoxicosis increased excretion of 17-hydroxycorticosteroids and 17-ketosteroids. After normalization of the function of the gland after iodine or thiouracil administration or after surgical treatment the excretion of corticosteroids was reduced. But upon studying on women suffering from hyperthyroidism the excretion in urine of 17-ketosteroids and creatine as a result of treatment, Kellen /379/ discovered the disappearance of creatinuria and could not determine any considerable changes in the excretion of steroids. It has been previously noted that, according to the results of Hungarian scientists, the secretion of the adrenal cortex in hyperthyroidism does not change quantitatively, but qualitatively: the formation of new compounds in the adrenal glands, which were not secreted from the adrenal glands of healthy persons, was determined in hyperthyroidism. But the exact nature of these compounds is not known.

Bastenie and Ermans /205, 206/ discovered that cortisone inhibits the enhancing effect of thyroxin on oxygen consumption and on the disappearance of P^{32} from erythrocytes (labeled in vitro) injected into the blood of hypophysectomized rats. The action of triiodothyronine was not reduced by cortisone under similar conditions. The authors conclude from this that cortisone suppresses the transfor-

Yu. B. Skebel'skaya notes in another work /130/ that the action of cortisone on the thyroid gland is not identical to that of ACTH. Unlike the corticotropic hormone, cortisone does not suppress the thyrotropic function and increases the goitrogenic action of methylthiouracil.

By studying the reaction of the thyroid epithelium of puppies to the administration of cortisone and ACTH, A.A. Voitkevich /33/ brought morphological proofs of the stimulation of the thyroid gland. He observed intensive local transformations of the thyroid cells, and of whole follicles in the pale insulas of the parafollicular cells, during the increase of the secretory activity under the action of cortisone. A part of the experimental animals exhibited increased differentation and new formation of follicles in thyroid tissue under the influence of ACTH.

But contradictory results exist on the action of the corticotropic hormone on the thyroid gland. S.P. Nikolaichuk and B.S. Rodkina /107/ pointed out that ACTH does not provoke stimulation of the thyroid gland and that increase of the corticotropic hormone production (hypertrophy of the adrenal glands) takes place upon prolonged administration of TSH, which inhibits the stimulation of the thyroid gland by the thyrotropic hormone.

Studies have shown that male and female gonads and the hormonal products of the adrenal glands may change the function of the thyroid gland. Gannong and Hildegard / 317/ note a considerable reduction of the I^{131} absorption in castrated dogs. It has been reported that estradiol, estrone, and diethylstilbestrol suppress the absorption of radioiodine by the thyroid gland of rats maintained on a diet with a low iodine content.

Aron, Gondar and Asch /186/ noted a reduction of the activity of the thyroid gland in the spring-summer period and the average activity in castrated rats was lower than in intact ones. Ogawa and others /444/ found different changes of the I^{131} absorption by the thyroid gland after castration· in castrated male rats the capture of iodine was increased and in females it was reduced. Money et al. /426/ studied the influence of various steroid hormones on the accumulation of radioiodine by the thyroid gland of rats

Previous studies in this direction often gave contradictory results, because of different experimental conditions. The results obtained on the absorption of radioiodine showed that ACTH and cortisone provoke the suppression of the thyroid gland function. A similar action was noted upon administering A compounds (dehydrocorticosterone) and a series of other estrogenic substances. Testosterone, estrone, progesterone, and other steroids also led to the reduction of I^{131} accumulation by the thyroid gland. Ogawa and his co-authors, administering various hormones to rats, came to similar conclusions.

Money and others discovered changes of the character of the action and the effect of steroids depending on changes in the diet. It was also noted that cortisone and ACTH suppress the capture of I^{131} in response to the action of the thyrotropic hormone, but have no influence on the growth of the gland cells. Migeon and others /419/ point out that in adrenalectomized rats maintained on desoxycorticosterone a reduction of its excretion in urine and feces was noted besides the reduction of the I^{131} absorption during the action of cortisone. *During this time the* I^{131} *content* in the blood was increased. There were no differences in the ratios of the fractions of iodinated components in the gland between this group of rats and normal ones. The mode of steroid action on the absorption of radioiodine by the thyroid *gland is not* yet known. They may have a direct influence or they may effect it through the pituitary. On the other hand, it is known that an increase of the *kidney iodine clearance is noted during* treatment with cortisone. But evidently this cannot itself explain the considerable reduction of the iodine absorption by the thyroid

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function of the thyroid gland in liver diseases by means of radioiodine On the basis of their studies and of published results the authors come to the conclusion that the liver may show its regulating influence either by the excretion of thyroxin from the blood into the intestine or by its destruction as a result of deiodination, or by way of inactivation as a consequence of the formation of compounds of the thyroid hormones with glucuronic acid. On the other hand, during liver diseases its diffused affection may become the cause of the changes in plasma protein structures, which will have an influence on the transfer of thyroxin in the blood and will cause in this way a change of the hormone penetration into the cell, and thus change its action in the tissue.

mation of thyroxin into triiodothyronine, which has a greater hormonal activity in the peripheral tissues.

Thus, published results on the action of corticosteroids on the function of the thyroid gland are basically similar, showing the suppression of the thyroid gland activity. This deduction is confirmed by clinical observations on the use of ACTH and cortisone during thyrotoxicosis.

The thyroid hormones in their turn influence the metabolism of corticosteroids in the organism. Yates et al. /619/report that triiodothyronine augments the total capacity of the liver to restore the cortisone A ring and that thyroidectomy reduces it. According to these authors, this takes place as a result of the reduction of the enzyme activity (Δ^4-steroid of dehydrase) or because of an insufficiency of co-enzyme—reduced TPN—and gives an enzymatic basis to changes of the biological half-life period of corticosteroids in hyper- and hypothyroidism.

Lacroix and Leusen /387/, who checked changes of tissue respiration of myocardial and diaphragm sections under the action of thyroxin and cortisone, noted antagonism in some tissues and synergism in others.

There are early works by A.N. Petrova /110/ on the influence of hormonal factors on the iodine content of the thyroid gland and the blood. She determined that rabbits exhibit a sharp reduction of the iodine content in the gland under the influence of folliculin and that the secretion of the iodine compounds in the blood is reduced. Insulin somewhat increases the iodine in the thyroid gland and reduces it in the blood, as a consequence of inhibiting the iodine secretion from the gland. A sharp increase of iodine in the thyroid gland and in the blood were noted under the influence of adrenalin. These results, obtained as early as 1937, were not confirmed by other researchers.

Some results exist on the interrelations between adrenalin and the thyroid gland. According to the observations of a number of authors, administration of adrenalin to rats provokes a reduction of the I^{131}-absorption by the thyroid gland. In adrenalectomized animals adrenalin considerably augments the absorption of I^{131}.

Ogawa et al./443, 444/ made extensive studies on the absorption of iodine by the thyroid gland after removal of the other glands of internal secretion, or after administering hormones of these glands to the animals. After adrenalectomy they determined an augumentation of the I^{131} in female thyroid glands Most corticosteroids, upon being administered to adrenalectomized animals, provoked a further reduction of absorption, but upon administering them in large doses absorption increased.

Utevskii and Butom /153/ studied the influence of thyroidine on the metabolism of adrenalin in the skeletal muscles. They showed that prolonged administration of thyroidine leads to the disappearance from the muscles of reversibly oxidized forms of adrenalin-like substances.

As may be seen from the above results, the question of the interrelations of the thyroid gland with other glands of internal secretion is still far from being answered. Detailed information exists only in regard to the interrelations of the thyroid gland with the pituitary, while on the question of its interrelations with other endocrine glands our information is fragmentary and not always uniform.

Some peripheral organs also take part in the regulation of the thyroid gland function. In this context the liver occupies a special position. The role of the liver in the peripheral regulation of the thyroid hormones was studied in considerable detail by Vannotti and Beraud /593/, St. M. Milcu et al. /100/. They studied the

results of Kassenaar et al./376/, thyroidectomized rats maintained on a daily dose of 6μg thyroxin have a considerably lower concentration of PBI in the serum at 4° than at 21 or 36°; in normal rats, on the other hand, the level of PBI was found to be higher at lower temperatures than at higher ones.

The study of oxygen consumption thyroidectomized rats receiving thyroxin and adrenalin at temperatures of 10, 18, 30° showed that thyroxin increases the calorigenic action of adrenalin at low temperatures, and this is the basic role of the thyroid gland hormone in adaptation to cold /402/.

A number of authors /615, 251/ studied the influence of prolonged exposure to cold on thyroxin secretion and on the rate of the thyroid gland hormone cycle, upon keeping rats at a temperature of 5° for 1 to 180 days. It was found that, after having lived for two weeks at a low temperature, the secretion of thyroxin increases considerably and the rate of the thyroid gland hormone cycle is also augmented. The thyroid gland has a definite regulating effect on oxygen consumption during a drop in temperature. Thus, removal of the thyroid gland from rats maintained at a temperature of 5° reduced the oxygen consumption to a minimum by the 8th day and at a temperature of 28° this level was reached by the 12th day /361/

The action of total irradiation of the organism on the function of the thyroid gland was also studied /228/. Upon exposure to 800–1000 r an increase of the I^{131} was observed after two hours; the increase was maintained for 24 hours and was then reduced.

Large radiation doses also increased the absorption of radioiodine, but a certain reduction set in at the beginning of exposure, which may be explained by the increased secretion of the hormones of the adrenal cortex.

It is interesting to note that exposure of mice to darkness stimulates the function of the thyroid gland, which is proved by the growth of the gland and by the increase of the I^{131} absorption /464/, on the other hand, exposure to light provokes an inverse effect. Guzek and Mach /336/ found that in rabbits maintained in the darkness for a long time the content of iodine in the blood increased and its content in the thyroid gland was decreased.

Various influences provoking stress led to the reduction of the capture of iodine by the thyroid gland. Thus, for example, the injection of formalin, as well as surgical intervention, suppressed the accumulation of iodine in the thyroid gland.

V. P. Dyskin (56), studying the influence of surgical trauma on the functional state of the thyroid gland, notes that the suppression of absorption was related to a state of pain during and after the operation, but occurred also without it. Very strong emotional influences sometimes had an influence too. According to his results, in various periods of the postoperative period the I^{131}-accumulation rate was maintained within normal limits. Changes of iodine accumulation by the thyroid gland under the influence of surgical trauma may be manifested in the stimulation of I^{131} accumulation, or in a transient inhibition with subsequent prolonged stimulation, or in severe and prolonged inhibitions. The state of stimulation and inhibition of the thyroid gland function is closely related to the central nervous system.

A change of the protein bound iodine content of the serum was noted after fever- and electroshock therapy /438/. Badrick et al /197/ made studies of the I^{131} absorption by the thyroid gland of rats after they had been swimming in water at a temperature of 15 or 40° for 10–15 min., after electroshock, and after intraperitoneal injection of adrenalin. All these effects provoke a suppression of the I^{131} absorption by the thyroid gland in intact, as well as in hypophysectomized and adrenalectomized rats. The suppression of thyroid gland function after electroshock and after

Chapter VIII

THE INLUENCE OF VARIOUS FACTORS AND PHARMACOLOGICAL AGENTS ON THE FUNCTION OF THE THYROID GLAND

(vliyanie razlichnykh faktorov i farmakologicheskikh agentov na funktsiyu shchitovidnoi zhelezy)

It is well known that various and numerous factors have an influence on the morphology and function of the thyroid gland. It is easy to influence the thyroid gland by changing dietary conditions, or by acting on the hormonal status of the organism. Various influences on the functional state of the organism within physiological limits, or in relation to stress, are easily reflected in the function and morphology of the thyroid gland. Many chemical agents having a specific influence on the state of the thyroid gland have been described during the last years.

1. The Influence of Changes of the External Environment on the Thyroid Gland

One of the external factors influencing the thyroid gland is temperature A number of authors report that exposure of laboratory animals to cold provokes the stimulation of thyroid gland function /546, 237, 586/ The secretion of the thyroid gland is increased during cooling, when there is need for increased metabolism

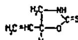
The influence of temperature on the thyroid gland was shown by histological methods — by the augmentation of the height of the follicular cells, as well as by the increase of absorption and of the radioiodine cycle. It was demonstrated by studies on animals with a sectioned brain stem that this stimulus is effected by way of acting on the center of temperature control in the mesencephalon /587/ As it was shown that animals subjected to cold need greater quantities of thyroxin in order to ward off the goitrogenic effect of thiouracil than when they are subjected to heat, this may express an augmentation of the demand for the hormone by peripheral tissues /262/ This demand is expressed by the stimulation of the thyroid gland by the mesencephalon and the pituitary.

Studies have recently been made on the influence of severe hypothermia on the function of the thyroid gland in experimental conditions. The study of the absorption of radioiodine by the thyroid gland of rats upon maintaining body temperatures between the limits of 16 to 39°, made by Audjus, showed that the lower the body temperature, the weaker is the capture of iodine by the thyroid gland (194). The main quantity of fixed iodine is in an organically bound form, mainly in the form of monoiodotyrosine and diiodotyrosine.

A similar result was obtained by Verzar and his co-authors/595/, and by Mach and Toczycky/402/, on rats during hypoxic hypothermia. At a body temperature of 15–20° the thyroid gland was not at all capable of absorbing radioiodine At a temperature of 25–28° the activity of the gland was somewhat reduced. External temperature also influenced the quantity of the serum PBI. According to the

He noted that when animals are deprived of water and food, this leads to a considerable reduction of the function of the thyroid gland. The antidiuretic hormone had no influence on the rate of hormonal iodine secretion.

Changes of the thyroid gland function were also provoked by the administration of excess quantities of cabbage, turnip, and soybean. These reports, made at the end of the 1920's, were thoroughly re-examined by Astwood /190/. He studied 61 types of alimentary substances from the aspect of their influence on the function of the thyroid gland. A study was made of the goitrogenic action of large quantities of these products administered with the food, as well as of their extracts. The results obtained from extensive works permitted Astwood to conclude that some vegetables, as for example cabbage, lettuce, rutabaga, strawberries, swede, reduced the capture of I^{131} when applied in large quantities. Yellow turnip has a particularly strong action: its simple water extract contained a substance suppressing the function of the thyroid gland in rats and humans. It was possible to separate from it 1-5-vinyl-thio-oxazolidon, having 1/5 of the activity of thiouracil on rats and the same activity as thiouracil on humans /192/.



The author also found analogous compounds in all other goitrogenic plants. As is pointed out by Astwood, these compounds are probably in a bound state in the plants and are liberated by an enzymatic method in a water solution. Other compounds with antithyroid properties were also separated from plants. It is still difficult to [illegible]

trogenic agents in the milk of cows fed with one type of Brassicaceae.

Studies were also made on how the iodine metabolism is influenced by food which consists mainly of certain single food stuffs. A.I. Stolmakova and others /136/, studying the diet of the population in localities with endemic goiter, discovered a disorder in the adequate ratio of proteins, fats, and carbohydrates in the diet and some limitations as to the choice of the alimentary products. In an area of marked goiter distribution it was found that there is a reduced vitamin C content in the vegetables and green foodstuffs, as well as a small quantity of Ca, K, Mg, Na, P in the food and an increased content of Ag, Cu, Sr. and others in the vegetables.

A.I. Shtenberg and I.A. Kusevitskii /170/ found considerable functional changes in rats maintained mainly on a carbohydrate diet during exposure to cold and overexhaustion. When these conditions were combined with iodine insufficiency in the food, severe morphological changes took place in the rats, with augmentation of the dimensions of the gland and its hypofunction.

N.V. Verzhikovskaya /26/ showed that a prolonged homogeneous meat diet provokes hyperfunction of the thyroid gland of rats.

Climak and others /246/ studied the influence of various quantities of protein in the diet on the iodine metabolism of the thyroid gland and determined that rats maintained on a diet with a high protein content accumulate somewhat more I^{131}, 24 hours after administration, than control animals. A low protein diet (7.3% of caseins) sharply reduces the accumulation of I^{131}. There are reports to the effect

administration of adrenalin was found to be temporary and disappeared speedily. The authors showed the reduction of absorption only in vivo and could not note changes in the absorption of iodine by sections of the thyroid gland.

Studies were made of the influence of muscular efforts on the thyroid gland hormone content of the blood and on the rate of excretion of injected thyroxin in healthy persons /392/ Determination of the butanol-extractable iodine of the serum and of the PBI and the radioactivity of the serum showed that muscular effort did not provoke clear changes of the serum hormone content, i.e., walking for considerable distances or swimming for 13 min. had no noticeable effect on the use of thyroxin by the tissues, which would have been reflected in the peripheral concentration of the hormone. But it was determined by studies on thyroidectomized rats that muscular efforts speed up the disappearance of thyroxin from the blood and from the organs of the gastrointestinal tract /285/. This observation probably reflects the existing changes most correctly.

Yu. B. Skebel'skaya studied the activity of the thyroid gland in rats under the influence of an auditory stimulation. Upon using a bell once she could determine a response, but prolonged use had an inverse effect.

[illegible]

increase of metabolism. In its turn, hypercompensation provoked a reduction of thyroid gland activity. Thus, the hypofunctional state of the thyroid gland during hypoxia is a response reaction of the organism to an increase of gaseous metabolism.

2. The Influence of Nutrition on the Thyroid Gland

The influence of a diet deficient in iodine has been subjected to repeated studies. The thorough works of Catz, Rawi, Gaiger /237/ are of considerable interest in this respect. Studies were made of the influence of a diet containing an insufficient quantity of iodine on the PBI, on the total iodine of the thyroid gland, on the weight of the thyroid gland, and on the capture of I^{131}. The animals were killed 10, 20, 34, 106, and 237 days after being maintained on such a diet. After 10 and 20 days, when the quantity of iodine in the thyroid gland was respectively 81 and 61% of its normal value, an increase of the I^{131} capture was noted. But even after 105 days of being maintained on such a diet, when the total iodine in the thyroid gland was under 20% and the PBI was at about half the level of the control animals, the gland did not increase in weight. Consequently, metabolic changes set in considerably sooner than the appearance of morphological changes in the tissues of the gland. Even during the whole observation period of 237 days it was not possible to determine an augmentation of the growth of the thyroid gland tissue.

Milcu and others /422/ report that in rats maintained for a long time on a diet poor in iodine the absorption of iodine by the thyroid gland was 10 times smaller than in the control animals and the time of excretion of iodine from the organism was shortened. Morphological changes were also noted in the gland of the experimental animals.

There are many works devoted to the influence of various alimentary factors on functional and morphological states of the thyroid gland, especially in relation to their possible etiological importance in the development of goiter; but studies on the influence of alimentary conditions on the absorption of radioiodine by the thyroid gland were also made without having this aspect in view. Reichlin /471/ studied the influence of lack of water, of starvation, and of the antidiuretic hormone on the activity of the thyroid gland and on the rate of secretion of the injected I^{131} from the gland.

L.M. Tsofina /30/ discovered an augmentation of the bromine content during thyrotoxicosis, as compared to its content in the normal thyroid gland.

B.M. Gordienko /47/ administered to rats subcutaneously 3 or 30 mg of NaBr per 100 g of weight for 25 days and noted a growth of the thyroid gland, changes characteristic of hypothyroidism, and a reduction of the basal metabolism.

Many and repeated studies were performed on fluorine in the etiology of endemic goiter and on the influence of its salts on the function of thyroid gland. It has been reported that administration of large doses of fluorides provoke a noticeable reduction, which is maintained for a long time, of the various parameters of the biological activity of the thyroid gland. Some authors attribute a definite importance to fluorine in the etiology of endemic goiter /49, 61/. It was shown that the thyroid gland has a marked affinity for fluorine and absorbs it in considerable quantities.

R.D. Gabovich and N.V. Verzhikovskaya /38/ note that administration of fluorine provokes an impoverishment of iodine in the thyroid gland,once fluorine accumulates in the thyroid gland it may compete with iodine by forming fluorotyrosines, which leads to an endogenous insufficiency of iodine The same authors showed by experiments that in rats receiving large quantities of fluorine the absorption of iodine did not differ from its absorption by control animals. Noticeable pathological changes in the thyroid gland only set in when water is used with a concentration of fluorine of 10-15 mg per liter, or of 0.75-1 mg of fluorine per one kg of weight. Such concentrations almost never enter the organism and this is why the authors do not accept the opinion of some researchers about the role of fluorine in the etiology of endemic goiter.

A number of other researchers /17, 151/ also think that the goitrogenic role of fluorine is unimportant. S.N. Cherkinskii and R.M. Zaslavskaya /165/ summarized the results available on the ratio of iodine to fluorine in the drinking water in various endemic centers of the Soviet Union. They noted that the F/I ratio is always above 30. Upon studying endemic centers of goiter no greater quantity of fluorine was noted in the external environment. An F/I ratio above 30 does not lead to a higher frequency of endemic goiter.

I.N. Sharkevich /166/ is of a different opinion; he determined the reduction of the I^{131} absorption and other functions of the thyroid gland in rats maintained on a diet with a high fluorine content. He admits the possible role of fluorine in the development of endemic forms of goiter.

B.B. Rodyanskii /116/, feeding rats with food containing 4.5 mg of sodium fluoride per 100 g weight of the animals, could note a lowering of the basal metabolism and secretion of the thyrotropic hormone. He affirms that F may have an antithyrotropic action.

Jenzer /369/ studied the influence of fluorine on the function of the thyroid gland of rabbits. Two months after administering various doses of fluorine to rabbits (one mg and more, every 24 hours) he determined a reduction of the basal metabolism, of the thyroxin content in the posterior lobe of the pituitary, and a suppression of the thyroid gland secretion.

Minder and Gordounoff /425/ tried to determine the presence of an antagonism between fluorine and iodine by way of adding fluorine salts to solutions of diiodotyrosine. It was shown by chromatographic studies that under these conditions diiodotyrosine is transformed into monoiodotyrosine. According to the author's opinion, this may explain the reduction of the radioactive iodine absorption by the thyroid gland upon simultaneous administration of large quantities of fluorine.

that during a diet with insufficiency of phenylalanine the thyroid glands of rats are small, but the mechanism of this action is still unclear.

3. Pharmacological Agents Having an Influence on the Thyroid Gland

A large number of chemical compounds having an inhibiting action on the function of the thyroid gland are known at the present time. In a series of cases such an action has a specific character and such substances have a practical use for controlling the function of the thyroid gland, in laboratory conditions as well as in the treatment of increased activity in people. The substances of this group are called antithyroid or thyrostatic compounds. Apart from them elements of group VII, as well as other inorganic and organic compounds, are known to have an influence on the function of the thyroid gland.

The influence of haloids

Isler, Leblond, Axelrod /364/ studied the influence of NaCl on mice maintained on a low iodine diet. Increase of the thyroid gland size and a low iodine content in it, as compared to the gland of control animals, were found in animals receiving complementary NaCl. Such an action of NaCl is explained by the increase of iodine excretion in urine under the influence of large quantities of common salt. Other reports exist about the weakening of the thyroid gland function and the strenghening of the thyrotropic function of the pituitary upon administering excess quantities of sodium chloride.

The interrelation between bromine and iodine in the thyroid gland and its influence on the functional state of the gland have been studied by many authors. The actual state of the question of the biological role of bromine is discussed in the recently published review by F. Ya. Berenshtein /20/. The thyroid gland of man contains 0.9-1.4 mg% of bromine. *After administering preparations of iodine the* bromine content in the gland is reduced. Administration of thyroid gland preparations provokes a reduction of the bromine level in the blood. Bromine, in its turn, has a considerable influence on the function of the thyroid gland.

E.N. Emel'yanova /57/ showed experimentally that the hormone is kept back by the thyroid gland and the quantity in the blood is reduced upon administering bromine.

Yu.B. Skebel'skaya /126/, who administered 10 mg of bromine to rats for 1-3 days, observed a decrease of the function of the thyroid gland and after longer administration a strengthening of its function.

The action of bromine is effected through the thyrotropic hormone of the pituitary. A report exists on the favorable influence of bromine preparations during [illegible] of the thyroid gland. Yagi, Michel and Roche /618/ note that the [illegible] ne is considerably smaller than [illegible] r administration of small doses. [illegible] d the authors could not determine any antagonism between bromides and iodides. Their metabolisms takes place independently. Bromine absorbed by the thyroid gland is not in a bound state; it does not enter into the composition of an organic compound and is speedily excreted The dehaloidizing enzyme of the *thyroid gland has the same action on bromotyrosine* as on mono- and diiodotyrosines.

I.N. Verkhovskaya /29/ affirms that bromine accompanies iodine and enters into competing relations with it in the thyroid gland. I.N. Verkhovskaya and

As is seen from the curve, the percentage of iodine absorption by the thyroid gland is first of all a function of the quantity of iodine administered. It is necessary to take into account the quantity of iodine in the food when evaluating the action of administered doses of stable or radioactive iodine.

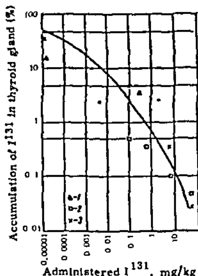


Figure 5. The dependence of iodine Accumulation in the Thyroid Gland on the Total Quantity of Iodine Administered

1—man; 2—rabbit; 3—rats

Bois and Larsson /224/ studied the action of different levels of iodine consumption on labeled iodine fractions in the thyroid gland after administration of I^{131}. It was shown that in rats, maintained for a long time on a diet with a low iodine content, iodine is accumulated more rapidly and in a greater quantity by the thyroid gland, and is secreted more rapidly from it, than in animals receiving a complementary quantity of iodine in their diet. The processes of reduction of monoiodotyrosine and diiodotyrosine fractions and the augmentation of thyroxin and triiodothyronine in the composition of thyroglobulin, which take place with time, have a more rapid course in rats maintained on a diet insufficient in iodine. Insufficient iodine consumption led to a considerable increase of the ratio of I^{131}-monoiodotyrosine to I^{131}-diiodotyrosine, as well as of the ratio of I^{131}-triiodothyronine to I^{131}-*thyroxin*.

Halmi /340/, determining the effect of various quantities of stable iodine on the absorption of I^{131} by the thyroid gland, discovered that administration of up to 100 mg of iodine has no noticeable effect on the concentration gradient of radioiodine $\frac{\text{thyroid gland}}{\text{serum}}$ in normal rats and in rats receiving propylthiouracil. Further increase of the quantity of stable iodine reduces this gradient in rats receiving propylthiouracil. This probably depends on the limited capacity of the thyroid gland for absorbing iodine. Values of the iodine concentration in the serum, required for the liquidation of the gradient, depend on the state of thyrotropic regulation.

Iodine administered to rats in doses from 1 to 100 mg penetrates very weakly

Demole /260/, who earlier affirmed the existence of an antagonism between *fluorine and thyroxin*, later admitted the incorrect nature of his previous conclusion and refuted the existence of a physiological antagonism between the hormone and the haloid.

On the basis of preliminary experimental results on the suppression of the thyroid gland function by fluorides, Galetti and co-authors /316/, and others, studied the function of the thyroid gland of patients suffering from hyperthyroidism receiving daily doses of 1-10 mg of sodium fluoride at various intervals. They did not succeed in determining a constant action of fluorides on the function of the thyroid gland. A number of the indicators of the activity of the gland were decreased. Clinical ameliorations were noted in a small number of patients.

Very recent results obtained as a result of the use of radiofluorine on rats /600/ did not confirm the previous chemical results of Chang and others /240/ on the accumulation of this element in the gland. Galetti and Yoyet /315/ too, could not determine noticeable absorption of radiofluorine by sections of normal or thyrotoxic glands. According to these authors, fluorine inhibits the absorption of iodine by the thyroid gland in the same manner as perchlorate, but to a lesser extent.

Apart from haloids, the thyroid gland also has a rather high activity in relation to other elements of group VII of Mendeleev's periodic system. Barman and others /203/ studied the concentration of manganese, technetium, rhenium, and bromine in the thyroid gland after administration of radioactive isotopes of these elements. Two hours after injection to rats the concentration of Mn^{54} in the gland is 10 times higher than its concentration in the blood, that of Br^{82} 1.3 times higher, and that of Tc 10-30 times higher, the capacity of the thyroid gland to absorb I^{131} and Re^{186} is more or less identical and is considerably higher than activity in relation to Mn and Br.

Another element of this group, astatine, also accumulates in the thyroid gland. Schellabarger and Godwin /519/ administered radioactive astatine intraperitoneally to rats and discovered its selective accumulation in the thyroid gland. The intensity of its inclusion became uniform upon shortening the time between administration and study. In rats receiving thiouracil the absorption of astatine by the thyroid gland increased, while the absorption of I^{131} was reduced under these conditions.

Barson and Schellabarger /204/ compared the efficiency of At^{211}, radiating α-particles, with the new short-lived isotope of iodine I^{132}, recently introduced into clinical and laboratory practice, in relation to their efficiency in inhibiting the I^{131} capture by the thyroid gland. It was shown that the same inhibition of the iodine absorption by the thyroid gland is obtained by using I^{131} in doses 2.8 times higher than the dose of At^{211}.

The action of iodide

Iodide is a well-known inhibitor of the thyroid gland and it is widely used in clinical practice in the control of hyperthyroid glands. It is necessary to dwell in particular on the absorption of iodine by the thyroid gland, depending on the concentration of its ions in the blood or in the external environment in general. The quantity of iodine absorbed by the thyroid gland depends directly on its quantity in the blood. The more iodine there is in the food, the less is captured by the gland. The same may be said about the capture of I^{131} administered for experimental and therapeutic purposes. In the early studies of Hamilton /341/ it was already determined that the iodine accumulated in the gland depends on the total quantity of iodine administered. This dependence is represented by a curve in Figure 5 (taken from the book of S. Komar /83/).

from biopsy, treatment with iodides leads to involution of a hyperplastic thyroid gland in thyrotoxic patients /328/.

A number of hypotheses has been made on the influence of iodide on the normal course of hormone formation in the thyroid gland. According to the opinion of some authors, iodide effects its therapeutic action by way of preventing the absorption of iodine. Ya. M. Kabak and E.B. Pavlova showed that a sufficient concentration of iodide totally blocks the formation of organically bound iodine in a normal thyroid gland and in fresh sections of the gland.

Fawcett and Kirkwood /287, 528/ think that iodide has an action very similar to that of aromatic goitrogenic agents, competing with tyrosine for the capture of oxidized iodine. According to their opinion, oxidized iodine reacts with an excess of iodide and forms a complex $I^- + I_2 = I_3^-$, inaccessible to tyrosine.

Despite the fact that both theories have experimental proof, and on the basis of the fact that iodine insufficiency plays a role in the formation of its organically bound forms, it was shown that a hyperplastic thyroid gland of patients suffering from Basedow's disease contains an even greater quantity of iodinated thyroglobulin than a normal gland after successful treatment with iodine It is also assumed that during Basedow's disease iodide exerts its therapeutic action by suppressing the reaction of the thyroid gland cells to TSH. There is a number of indirect proofs in favor of this assumption; 1) iodide inhibits the action of TSH on the thyroid gland of hypophysectomized rats; 2) the in vitro inactivation of TSH by explants, 3) the thyroid gland itself is inhibited by iodide of the medium, while there is no active TSH in the urine of patients suffering from Basedow disease. It appears easily in the urine of thyrotoxic patients which have been subjected for a short time to treatment with iodide. Other results were also brought, confirming this opinion, but all these arguments do not constitute a final proof for the direct interaction of TSH with the cells of the thyroid gland and do not exclude other methods of interaction of iodine with the thyrotropic substance of the pituitary.

The action of other elements on the thyroid gland

In relation to the study of the etiology of goiter, a certain importance is attributed to the influence of microelements on the functional state of the thyroid gland. Detailed studies have recently been made on the cobalt, nickel, manganese, copper, and zinc contents of the thyroid gland and it was attempted to relate fluctuations of their quantity to the activity of the gland and to their possible importance in the etiology of goiter.

Bellotti and others /209/ studied the content and distribution of manganese in the thyroid gland and determined a relatively large quantity of this element in the gland, especially at an early age. The greatest part of the manganese was found in the colloid. After an intravenous injection of two mg of manganese during increased functioning of the thyroid gland, a high level of manganese was noted in the erythrocytes.

Koch and Smith /384/ determined the content of copper and zinc in the tissue of the thyroid gland in a normal state and in some pathological states They noted a sharp increase of the copper content and a threefold increase in the zinc content of the tissue of the gland in reticular carcinoma with lesion of the organ. In cancer without clear lesion of the thyroid gland and in adenoma they noted a relatively small increase of the copper content.

Rechenberger /470/ reported on the increase of the copper content of blood

into the thyroid gland. In the human organism noticeable suppression of iodine accumulation already takes place when 1-2 mg of iodine are introduced daily /298/. This suppression is particularly noticed in cases of hyperthyroidism. The quantity of iodine contained in iodinated salt and in some vitamin-mineral compounds is insufficient in order to reduce the uptake. But in fact, all other iodinated drugs reduce the absorption of iodine by the gland and the action of iodine preparations on absorption can continue for a period of several days in healthy subjects, to several months in cases of toxic nodular goiter. During prolonged administration of therapeutic doses of iodine the colloid content of the gland increases and the follicular cells become flattened and less active. But the mechanism of iodide action leading to the alleviation of thyrotoxicosis remains as yet unclear. There are three hypotheses on the method of action of iodine: 1) iodine has a direct action on the thyroid gland, suppressing the formation and secretion of the hormone and reducing the activity of the follicular epithelium; 2) iodine directly inactivates TSH and 3) iodine suppresses the secretion of TSH from the pituitary.

Most researchers think that iodine influences the function of the thyroid gland by changing the production of TSH. But there are a number of studies showing the direct effect of iodine on the tissues of the thyroid gland.

Thus, A.S. Breslavskii /22/ studied the influence of micro- and macrodoses of iodine on the thyroid gland of rats (40 μg of NaI or 50 mg of NaI per 100 g of weight) receiving 6-methylthiouracil and not receiving the antithyroid preparation. He did not succeed in showing changes of the TSH content in the pituitary under the action of iodine. In view of the fact that changes in the thyroid gland took place without changes of the TSH of the pituitary, the author thinks that iodine acts directly on the thyroid gland.

Greer and DeGroot /328/ determined the rate of hormone secretion of the thyroid gland in euthyroid and thyrotoxic persons who received 300 mg of NaI daily. In thyrotoxic patients iodine provoked a reduction of the secretion rate of the thyroid gland. Administration of varying doses of TSH when iodine continued to act restored the secretion rate of the products to its previous value. Iodine had no action on nonthyrotoxic patients. After they were given TSH iodide provoked the slowing down of the hormone secretion of the thyroid gland, just as in thyrotoxic patients. Thiouracil had no action on these processes. On the basis of the results obtained the authors conclude that iodide and TSH have antagonistic influences on several intrathyroidal mechanisms responsible for the secretion of the thyroid hormone. They also do not exclude partial influence of iodine on the secretion of TSH by the pituitary.

A.A. Voitkevich /32/ studied the influence of KI on the structure of the thyroid gland of rats, upon administering it simultaneously with sulfidine or thiouracil. When the animals received only potassium iodide in large doses with their food, deviations were observed in the microstructure of the thyroid gland and a simultaneous reduction of the biological activity of the thyroid tissue by 15%, as compared to the normal state. Upon administering KI to the animals, together with thiouracil or sulfidine, an augmentation was noted in the changes of the microstructure, as [illegible] experiments [illegible] Ya. M. Kabak [illegible] inistration [illegible] he pituitary under the action of thiouracil but, at the same time, iodide weakened the reaction of the thyroid gland to thioureates. Analogous results are brought by McGinty and Sharp /400/.

The action of iodide on the thyroid gland is completely different from the action of thiouracil and other goitrogenic agents. As was shown on tissues obtained

that while supplying a diet with a low iodine content calcium reduces the capturing of iodine by the thyroid gland and provokes morphological changes characteristic of a hypothyroid state. The absorption of iodine from the intestine remains unchanged after administration of a single dose of calcium or after its prolonged administration. $CaCO_3$ also had a goitrogenic effect during parenteral administration of iodine.

It is possible that the goitrogenic effect of calcium is realized by way of increasing the urinary iodine clearance, or by reducing the synthesis of thyroxin. N.S. Demidenko /50/, provoking disorders of the calcium metabolism by changing the functional state of the parathyroid glands, studied the goitrogenic effect on the thyroid gland. Upon increasing the calcium content of the blood, the reaction of the thyroid gland of rabbits to administration of methylthiouracil was somewhat increased. During this the thyrotropic function of the pituitary was considerably decreased. Thus, during calcemia clear inconsistencies are noted between the reaction of the thyroid gland to the goitrogenic factor and the intensity of the thyrotropic function. Upon reducing the calcium content of blood, no particular changes in the reaction of the gland to the goitrogenic factor were noted. A noticeable increase of the thyroid gland reaction to the goitrogenic effect was noted when rabbits received methylthiouracil for 15 days. Hypercalcemia was then provoked in them and administration of the goitrogenic substance was continued. During this the dimensions of the thyroid gland increased by 2.5 times, as compared to the control gland. Thus, under conditions of an iodine deficiency hypercalcemia considerably enhanced the development of goiter and, consequently, as is pointed out by the author, the disorder of calcium metabolism may strengthen the effect of iodine insufficiency on the development of goiter.

Szafran and Mach /403/, who studied iodine metabolism in the progeny of rats maintained on a diet with an excess of calcium, came to similar conclusions. In these animals various indicators of the functional state of the thyroid gland were decreased. In rats of a third generation raised on a diet rich in calcium the capacity of the gland to accumulate iodine was 6 times smaller than in the control animals. The authors come to the conclusion that prolonged administration of calcium, even when given together with a diet with adequate iodine content, provokes severe changes in the metabolism of iodine and causes disorder of the thyroid gland function.

4. The Action of Antithyroid Substances

Important results have been achieved during the last two decades in the chemical control of the function of the thyroid gland. During this period many effective substances, having an inhibiting action on the function of the thyroid gland, have come into laboratory practice and therapeutic use. This group of substances, which was named antithyroid or thyrotoxic substances, has a large number of representatives, related to several groups of organic and inorganic compounds. The most active components of this group were found to be sulfur-containing organic substances. At th[illegible] tion on the func[illegible] search for new [illegible] an overactive [illegible]

It is known that antithyroid substances inhibit the thyroid gland by interfering in the various phases of iodine metabolism in the gland, but the problem of their mechanism of action has not yet been fully determined in most cases.

The first report on the chemical control of the thyroid gland came out in the

serum in thyrotoxicosis and on its reduction in hypothyroidism in humans.

A large number of studies are devoted to the importance of cobalt for the function of the thyroid gland. The influence of this microelement on the function of the gland was studied in relation to therapeutic uses of cobalt preparations, one of them being vitamin B_{12} which contains 4.5 % of cobalt. Results on the effect of cobalt preparations on the function of the thyroid gland are not always uniform. Roche and Layrisse /501/, as well as Kriss et al. /385/ affirm that cobalt, administered orally, effects a constant suppression of the thyroid gland function. Sharkevich /167/, who studied the action of $CoSO_4$ on the absorption of I^{131} by the thyroid gland of rats, came to the same conclusions. According to his results, the thyroid gland has a higher sensitivity to cobalt than other organs. The selective accumulation of this element in the thyroid gland gives rise to the question of its possible role in the etiology of endemic goiter.

Vitamin B_{12} also has a certain relation to the function of the thyroid gland and to its hormone, which is not fully determined. There are reports of Borson and others /226/ that in the presence of a diet lacking in vitamin B_{12} hyperplasia of the thyroid gland appears in rats. Vitamin B_{12} totally prevents the appearance of a thyrotoxic state in chicks /31/

Contradicting results also exist. Thus, for example, Jaimet and Thode /365/, as well as Holly /355/, upon using similar therapeutic doses of cobalt could not discover any noticeable effect on the function of the thyroid gland. This question has been very recently restudied by Paley et al. /449/ on euthyroid and hyperthyroid patients, after administering cobalt chloride in a dose of 37.5 mg for over 10 days. A considerable reduction of the I^{131} absorption by the thyroid gland was determined after 30 min, 1 hour, and 24 hours. Subsequent administration of thiocyanate led to the expulsion of all the absorbed iodine from the gland.

These results mainly showed that cobalt blocks the organic binding of the administered radioiodine by the thyroid gland Results of studies on the distribution of $Co^{60}Cl_2$ showed that under conditions of stress only about 10 % of the administered cobalt is adsorbed from the gastrointestinal tract.

Differences in the adsorption and the level of cobalt in the blood and in the thyroid gland could have been the cause of conflicting reports on the effect of its therapeutic doses on the function of the human thyroid gland. Results of studies on rats did not give proof of a higher absorption of cobalt by the thyroid gland. Its quantity in the gland was found to be no greater than its content in the plasma of the organ.

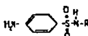
A large number of studies is devoted to the role of calcium in the etiology of endemic goiter. The possible influence of calcium on the development of endemic goiter is another old problem. The role of calcium as a goitrogenic agent has been discussed for more than 120 years, but there are as yet no results which confirm this convincingly. Several hypotheses exist about the possible mechanism of action of calcium on iodine metabolism. This action may be related to the precipitation of iodine in the intestine and to the prevention of its absorption by the increase of urinary excretion of iodine when calcium is contained in excess quantity in the food. It is also admitted that, in the presence of an excess of calcium, it is probable that the absorption of chlorides leads to the reduction of iodine absorption by the thyroid gland.

Taylor /570/, adding 2 mg of calcium carbonate to the food of rats, showed

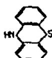
inhibition of growth, etc, i.e., a picture characteristic of the thyroid gland removal is observed. Hyperplastic changes in the thyroid gland also appear.



P-aminosalicylic acid



Sulfonamides



Phenothiazine

All these questions in respect to the various antithyroid substances were studied in detail by K.A. Voitkevich, Ya. M. Kabak, A.N. Petrova, M.G. Zaks, and others and elaborated upon in the monograph by Voitkevich, as well as in a series of surveys and separate articles /65, 60, 111/.

M.N Khanin, T.G. Terekhova,and E.I. Burshtein /158/ were among the first to study the action of thiourea on basal metabolism. They noted the absence of severe hypertrophy of the thyroid gland and changes of the follicles in dogs, as compared to rats in a similar state. In rats receiving thiourea basal metabolism was twice as low as in the control animals.

In another work M.N. Khanin and K.G. Ioffe /157/ also showed the high therapeutic effect of thiourea on patients suffering from Basedow's disease. Treating with thiourea led to the speedy reduction of basal metabolism.

Slingerland /531/ tested the influence of 180 compounds of various structure and pharmacological effect on the absorption of I^{131} by sections of sheep thyroid glands. Most of these compounds, including atropine, histamine, para-aminobenzoic acid, para-aminosalicylic acid, vitamins A, B_1, B_6 in concentrations of 10^{-3}M, had no influence on the gradient concentrations. Many compounds,which are difficult to classify by any distinctive feature, suppressed the absorption of iodine. Of these, mercuric chloride, methylene blue, rhodamine, ninhydrin, menadione, dinitrophenol, arsenic trioxide, reduced the concentration of the I^{131} which had already accumulated in the section. A large number of compounds inhibiting the absorption of radioiodine by the thyroid gland were found to be substances reacting with SH groups. Some of the tested compounds inhibited, together with the reduction of the I^{131} capture, the oxygen consumption of gland sections

Studies of the derivatives of thiazolidine, rhodanine, 5-methylrhodanine, and 5-o-chlorobenzylidenerhodanine made by S A Glova, M S Avgustinovich, L P Demkiv, and A. P. Dyban/43, 1, 51, 55/ disclosed the antithyroid and goitrogenic activity of the first two compounds, while their thyrostatic action was found to be considerably stronger than that of 6-methylthiouracil.

Studies on a number of new compounds were made during the last years Ya. M Kabak, I. B. Simon and A.S. Konikova /70/ tested the influence of twelve new compounds with the common group



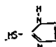
middle of the last century, when notice was taken of the sedative action of hydrocyanic acid on patients suffering from thyrotoxicosis. The next observation was made in 1932 by Marin and Bauman (cit. from The Hormones,/358/), who noted the inhibiting effect of methylcyanide on the thyroid gland of rabbits. A report then appeared on the development of goiter with reduced metabolism in patients suffering from hypertension and treated with thiocyanate /202/. But the progress of our knowledge on thyrostatic substances begins from the work of Mackenzie, Mackenzie,and Maccollum /406/, who reported for the first time in 1941 that sulfaguanidine is a goitrogenic agent in rats. A similar report was then made in regard to thiocarbamate. These discoveries provoked intensive study of the antithyroid action of the above compounds and stimulated the search for new inhibitors of thyroid gland function having no toxic effect on the organism. From the large number of compounds checked by Astwood in this respect /193/ thiouracil had the strongest activity.

A methylated derivative of thiouracil, which was found to be a considerably more active antithyroid substance than thiouracil itself, was tested in the laboratory of Kabak /66, 64, 72/. The number of antithyroid substances increased continuously and there are actually more than 50 known compounds having a thyrostatic effect, which are used to various extents in medical practice. In all, several hundreds of such compounds were synthesized. Most of them were found to be goitrogenic to a certain extent

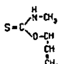
A considerable part of the antithyroid compounds contain in their structure a thiocarbamide group having an antithyroid effect. One group of derivatives contains thiourea, thiosemicarbazole, 2-mercaptoimidazole, compounds having an oxazolic structure, thiouracil and its derivatives, thiopyridine, etc.



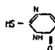
Thiourea



2-mercaptoimidazole



2, 5-vinyl-2-thio-oxazolidon



2-thiouracil

Another large group is composed of the derivatives of aniline, considered as being aromatic inhibitors of the thyroid gland. This group is represented by para-aminobenzoic acid, para-aminosalicylic acid, phenothiazine, amphenone, etc. A large number of sulfonamides, resorcin, parahydroxypropiophenone, etc , are also related to this group.

The third group of antithyroid substances is composed of inorganic ions.

Besides this, there is a number of compounds which cannot be related to any of these groups.

The above groups of antithyroid compounds differ by the variety of their action, by the mechanism of the thyrostatic effect, as well as by the comparative strength or degree of the morphological and biochemical changes taking place, not only in the thyroid gland,but also in other tissues The common factor of all these antithyroid substances is a reduction of the basal metabolism, a reduction of the frequency of heart contractions, morphological changes in the anterior lobe of the pituitary,

and the cells. Thus, the action of antithyroid substances of this group is summed up by the blocking of thyroxin synthesis in the gland.

There are reports on the influence of thiouracil and its derivatives on the metabolism of the thyroid hormones in the gland. Van Arsdell and Williams /589/ found that propylthiouracil slows down the destruction of I^{131}-labeled thyroxin and triiodothyronine in the organism of rats. A speeding up of the I^{131} excretion in feces is noted simultaneously and this is related to its augmented entry into the bile.

The study of the mechanism of action of 5-iodo-2-methylthiouracil /590, 326/ on rats showed that this derivative of thiouracil prevents the formation of thyroxin and probably increases the elaboration of TSH, which conditions the development of goiter.

Aromatic compounds, sulfonamides, para-aminobenzoic acid, para-aminosalicylic acid, resorcin,and others have a somewhat different action. There is an opinion that their influence on the function of the thyroid gland comes from the fact that these compounds compete with tyrosine for the binding of oxidized iodide. This opinion has been experimentally confirmed by the works of Fawcett and Kirkwood /287/. Disorder of the iodination of tyrosine leads to the blocking of the thyroxin synthesis and, from there, to chemical hypothyroidism

It was shown that sulfonamides do not have an inhibiting action on the capture of iodine by the thyroid gland. Recent studies of the mechanism of action of a new sulfonamide, carbutamide, also showed that this preparation suppresses the formation of organically bound iodine in the gland, without influence on the absorption of iodine by the thyroid gland.

The action of another antithyroid substance, thiocyanate (rhodanide), is of a completely different character. Its basic effect depends on its suppressing the capture of iodine by the thyroid gland in vivo and by its sections in vitro /307/. It was later shown that thiocyanate ejects iodide from the thyroid gland when the organic binding of iodine in the thyroid gland is blocked by the administration of thiouracil. Recent studies of Vinegaarden and others showed that some univalent ions as perchlorate, chlorate, hypochlorate, periodate, iodate, diiodate, and nitrate have properties similar to those of thiocyanate in the blocking of the iodine capture by the thyroid gland and in the ejection of iodine from the gland. These substances also have a certain goitrogenic action.

A.S. Breslavskii and I.B. Simon /23/, comparing the thyrostatic action of potassium perchlorate to 6-methylthiouracil, came to the conclusion that while perchlorate has a smaller goitrogenic effect, it has a considerably stronger antithyroid influence.

Considerable reduction of the I^{131} absorption during prolonged administration of perchlorate was also shown in a series of other works /234/. This property of perchlorate, in the absence of toxic side effects, makes it a most suitable means for the control of an overactive gland. Its use in the treatment of Basedow's disease had a good therapeutic effect.

A comparative study was recently made on the influence of various antithyroid preparations on the capacity of the thyroid gland to concentrate radioiodine. M.F. Merkulov /99/ administered perchlorate, 6-methyl-2-thiouracil, and 1-methyl-2-mercaptoimidazole to white rats for a prolonged period and then studied the absorption of I^{131} by the gland. It was shown that the thiouracil derivative increases the iodine content in the gland by 2.8 times and reduces its level in the blood considerably. The mercaptoimidazole derivative had a similar effect. Both preparations

on the absorption of radioiodine by the thyroid gland of healthy people. The high antithyroid activity of 2-mercaptoimidazole was confirmed, as in a dose 16 times smaller than that of methylthiouracil it caused total inhibition of the I^{131} absorption. *The methylated derivative of this component was found to be even more active.* It was also shown that amphenone--3,3-bis (para-aminochenyl)-butanone-2--, which probably has an influence similar to that of 2-mercaptoimidazole and blocks the organic binding of iodine in the thyroid gland, has antithyroid activity.

The effect of thyroid gland inhibitors is totally removed upon administering thyroxin, but this action is not related to peripheral neutralization of thyrostatic substances. As was shown by many studies, thiourea and similar antithyroid substances did not interact chemically with the thyroid hormones. There is also no proof of the change of response of the organism to the administration of thyroxin under the action of thyrostatic compounds. Consequently, antithyroid substances interfere in the function of the thyroid gland in the process of hormone formation.

Suppression of iodine absorption by the thyroid gland takes place under the action of thiocarbamides, e.g., thiourea, thiouracil, and other analogous compounds, the iodine content of the gland is also considerably reduced. Such observations were made in vivo and in vitro. Astwood and Bissel /193/ noted a reduction of iodine in the gland to 1/30 of the initial quantity. The reduction of the quantity of total iodine, as well as that of physiologically active iodinated compounds in the thyroid gland, *were also shown by means of bio-assay in the experiments of* Ya. M. Kabak /64/ by the implantation of thyroid glands of normal rats and of rats receiving methylthiouracil into tadpoles. As was expected, speedy metamorphosis of the tadpoles occurred after implantation of the thyroid gland of normal rats and the gland of rats receiving the antithyroid preparation decreased the morphogenetic activity. The basic action of thiourea, thiouracil, and its derivatives on the thyroid gland is expressed by blocking the process of hormone synthesis. It was determined that thiouracil prevents the binding of iodine absorbed by the thyroid gland into an organic form. Besides this, changes of the oxidizing-reducing potential of the colloid and the cells were observed. The changes observed under the action of thioureates bring to mind the action of KCN on the cellular enzymes.

Bois and Larsson /225/ studied the action of prolonged administration of propylthiouracil or *TSH to rats maintained on an iodine deficient diet.* Determination of the iodinated components in the thyroid gland revealed the reduction of diiodotyrosine formation. Notwithstanding studies that have been made, there is no definite opinion on the chemical site of the action of thiouracil. A hypothesis was advanced on the binding of free iodine by thiourea. We should then observe competition between tyrosine and thiocarbamides for elementary iodine. During this the capture [illegible] transform elementary iodine into iodide and

no convincing proof. Most researchers see the cause for the disorder of hormone formation under the action of thioureates as being the suppression of the function of the oxidative enzymatic systems, ensuring the transformation of iodides into I_2.

As was shown, this process is effected under the action of peroxidase and cytochrome oxidase. Their presence in the gland was determined by Dempsey /261/ in histochemical studies. According to his opinion, addition of thiouracil leads to the suppression of peroxidase activity, without touching the cytochrome system. De Robertis /263/ also maintains the same opinion.

An opposite point of view was expressed by another group of researchers, who discovered a disorder of cytochrome oxidase activity under the action of thiocarbamides. Besides this, as was shown by Dempsey /261/, De Robertis /263/, and Gross, thioureates provoked changes of the oxidizing-reducing potential of the colloid

preparations. Such an effect is observed even in cases when the preparation was administered to patients whose metabolic rate was close to that of a hyperthyroid state.

The problem of the metabolism of many antithyroid substances in the organism has not yet been determined and it is not excluded that the antithyroid effect may in a number of cases be created by the degradation products of these components in the organism.

It was very recently shown in respect to thiouracil that the process of its detoxication takes place in the organism by way of methylation at the 2-positions and that the administered compound is partly excreted in the urine in the form of 2-methylthiouracil /515/

According to the report of Maloof and Soodak /412/, thiourea is also speedily destroyed in the organism. Ten hours after administering 3 mg of a S^{35}-labeled preparation there was 10 times more activity in the gland of the rats than in the serum, but only 3.4% of the S^{35} was found in the form of thiourea in the thyroid gland and 75% in the serum. More than half of the S^{35} in the thyroid gland was in the form of a sulfate. Liver and thyroid gland sections absorbed thiourea and thiouracil, but capture against the concentration gradient did not take place and all the S^{35} in the sections remained in the same form in which it was administered.

There are only a few reports on the action of antithyroid substances on other aspects of metabolism in the thyroid gland, or on the processes of hormonal iodine metabolism in other organs. Notice should be taken of the report of Watson and Trikojus /602/, who succeeded in showing a considerable reduction of the proteolytic activity of the thyroid gland tissues of rats receiving 2-methylthiouracil. Bellotti and Ravera /210/ reported that upon administering propylthiouracil to guinea pigs a considerable reduction of the citric acid content of the gland takes place, together with the augmentation of the weight of the thyroid gland.

Many antithyroid substances are very important for the treatment of hyperthyroidism. Extensive experiments on the use of various preparations having a thyrostatic action show their considerable effectivity upon being administered for a prolonged period, but disappoint because of the constant relapses after the treatment has ceased. These preparations are nevertheless extensively used when preparing patients with toxic manifestations for surgical interventions.

Apart from definite antithyroid substances having a specific action on the function of the thyroid gland, there is a large number of pharmacological substances used in medical practice having a certain thyrostatic effect when used for other purposes. Many of these preparations are being studied in detail, in order to better control the functional state of the gland when they are used for treatment.

G.P. Smirnov /132/ studied the action of some blocking agents (substances disrupting the reflex arc at various points) on the tissue metabolism of the thyroid gland of mice and rats. A ganglionic preparation of hexonium in deliberate ganglion-blocking doses, sharply reduced the I^{131} content of the thyroid gland of mice, but hyperplasia of the gland was not observed. The blocking of the pituitary thyrotropic function probably also takes place under the action of hexonium. But hexonium, atropine, and sympathomimetine have at the same time no noticeable influence on the transformation of inorganic iodine into an organically bound form. They act on the inclusion of iodide into the tissue of the gland and hexonium also reduces the secretion of iodine from the gland. On the other hand, hexonium and atropine increased the inclusion of I^{131} in the thyroid gland and its secretion from it when administered in small doses. The reduction of various indicators of thyroid gland activity was determined upon administering cysteamine /292/ and a series of sedatives, as for example reserpine /386, 440/, promazine, meprobamate /440/, etc.

blocked the iodination of thyroglobulin. The capacity of the gland to accumulate iodine was sharply reduced upon administering $KClO_4$. Figure 6 gives a schematic representation of the character of action of some antithyroid substances.

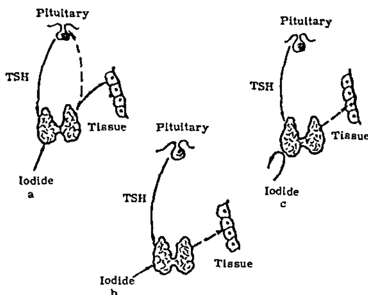


Figure 6. The mode of action for the thyroid hormones

a—in a normal state, b—action of thiocarbamides, sulfonamides, suppressing the synthesis of thyroxin; c—action of thiocyanate, suppressing the assimilation of iodides

Most of the above-mentioned antithyroid agents have a goitrogenic action, which is expressed by hyperemia, hypertrophy of the thyroid gland, by an increased height of the epithelium, by resorption of the colloid, etc. As became known later, this reaction of the thyroid gland is a secondary compensating mechanism, effected by the participation of the thyrotropic function of the pituitary. The formation of the thyroid gland hormones is reduced by the action of thiouracil, their level in the circulating blood is sharply lowered, and this leads to the removal or to the considerable weakening of their action on the anterior lobe of the pituitary. As a result of the weakening of the control of the pituitary thyrotropic function, production of TSH increases and a characteristic "goiter reaction" appears in the thyroid gland. Although such an interpretation of the mechanism of goiter reaction has no direct proof, there is no doubt that it is at least partly correct. The following fact confirmed this assumption: in hypophysectomized animals administration of thiourea, sulfaguanidine, thiouracil, and other antithyroid substances does not provoke a goiter reaction; in animals becoming goitrous after receiving thiouracil, TSH is not found in the pituitary and during the suppression of the thyrotropic function of the pituitary (starvation at high temperatures) no such goiter reaction was observed.

But there is a series of factors contradicting the above interpretation of the causes of the goiter reaction. It was shown, for example, that there is an increase of the height of the thyroid gland cells of animals, within 24 hours after the beginning of thiouracil action, before the PBI of the plasma had been reduced to a considerable extent. Besides this, it was demonstrated that thiouracil and analogous compounds, upon being administered together with TSH, increased the action of the simultaneously administered thyroid stimulating hormone. Such an increase of the TSH action by the above agents may be explained by the augmentation of the goiter dimensions, which were observed in some patients treated with one of these

methods of chemical protection from internal ionizing radiation. The results of these studies show the identity of the physiological aftereffects of the destruction of the gland by radioactive iodine to those setting in after surgical thyroidectomy. The authors note total reversibility of the manifestations of the antithyroid state in ducks, as well as in rats, upon compensating the lacking natural hormone with exogenous thyroidine. Blocking of the thyroid gland with stable iodine or with derivatives of thiocarbamide, a short while after administration of radioiodine, was an effective method for protecting the endocrine organ of the experimental animals from radiation.

According to a recently published work, A.A. Atabek /15/ studied the biological action on rats of radioactive iodine administered by various methods. The author notes that upon administering a dose in portions inhibition of the function of the thyroid gland is considerably less manifest than when the same dose is given at one time.

The destruction of the thyroid gland by large doses of radioactive iodine provokes a series of changes in the formation and secretion of hormones from the gland. Reports have been published about the fact that after administering therapeutic doses of I^{131} the blood shows noticeable quantities of organic compounds of iodine, mono- and diiodotyrosines, and triiodothyronine which are insoluble in butanol But it still remains unclear whether these products appear as a result of the radiation on the thyroid gland. New studies have been made by Benua and Dobuns /211/, Horst et al. /359/. It was noted in the first work that when radiotherapy gives good results the rate of radioiodine loss from the gland increases two weeks after the administration of I^{131}. Usually 20-60% of iodine still remain in the gland for 10-15 days and when a favorable effect is obtained it is reduced to 2-10%. In patients receiving a large dose of irradiation of the thyroid gland the quantity of the butanol-extractable radioactivity is reduced. These results are in accordance with those of Robins et al., proving the appearance of thyroglobulin in the blood of thyrotoxic patients who received large doses of radioiodine /474, 476/. The reduction of the fractions extractable by butanol might reach 50% and less by augmenting the iodine-containing component ,thyroglobulin, which is not extractable by butanol. It is assumed that this change is a direct result of the irradiation.

According to the results of Benua and Dobuns /211, 212/, triiodothyronine is found in the blood of most patients after administration of 10-12, 36-mC of I^{131} The authors do not relate the appearance of triiodothyronine to radiation. In a patient suffering from Basedow's disease 17 days after administration of 12 mC I^{131}, 17% iodide, 45% thyroxin, 14% triiodothyronine, 20% monoiodotyrosine, and 4% diiodotyrosine were found in the serum. Monoiodotyrosine was generally found more frequently in large quantities and it is not a result of the action of radiation or hyperfunction of the thyroid gland. Diiodotyrosine was found only after administering very large doses.

The results of Horst, Prevot, Franke /359/, are related to the synthesis of the thyroid hormones in patients receiving therapeutic doses of radioiodine The authors compare the quantity of hormonal iodine and the capacity of iodine of being replaced in the thyroid gland before and after treatment. The reserve of hormonal iodine in thyrotoxic patients was considerably reduced after treatment with radioiodine; average absorption values of the thyroid gland returned to normal, but the values of PBI in the blood increased considerably.

Studies of Sterling and Chodos /548/ showed that after treating thyrotoxicosis with radioiodine, as well as after surgical thyroidectomy, the rate of degradation of I^{131}-labeled thyroxin is reduced to its normal level, or even below it.

We studied the dynamics of the changes of radioactivity in the gland, blood, and

Slingerland /532/, Newman and Cupp /439/, studied the action of iodoalphionic acid (priodax), a preparation used in cholecystography, and found that it reduces the capacity of the thyroid gland to absorb iodine *until 30 days after its use.*

5. The Action of Radioactive Iodine on the Thyroid Gland

The capacity of the thyroid gland to absorb a large part of the radioactive iodine administered to the organism made it possible for clinicians and researchers to use iodine in order to change the structure and function of the gland radically. Radioactive *isotopes of iodine entering the gland are retained there just as the* atoms of stable iodine, but in their constant disintegration they liberate high-energy particles having a destructive action on the tissues of the gland.

The radioactive isotope of iodine I^{131}, with a halflife of 8.04 to 8.16 days, has been used almost exclusively for research and diagnosis since 1940. But during recent times another isotope of iodine, I^{132}, having a halflife of 2.26 hours, is beginning to assume practical significance /342/. But I^{132} with the same quantity of μC *irradiates the thyroid gland about 30 times less than* I^{131}. *The actual dose* of radiation on the gland from the same number of μ C administered is even smaller, for the quantity of radioactivity concentrated by the thyroid gland is limited by the speedy decomposition of the isotope. This difference in irradiation is an invaluable advantage of the new isotope for research on humans. This is why it is highly expedient to use I^{132} when it is necessary to make studies during pregnancy or on children. It is especially convenient to use this isotope when making repeated studies on one and the same person during a series of examinations of the function of *the thyroid gland, for example in order to evaluate its fluctuations in healthy peo*ple, or to study the effect of drugs on it /323/

As is seen from data published, the acquirement and the use of I^{132} for the determination of thyroid gland function is very simple and makes it possible to reduce the irradiation dose of the thyroid gland 40 to 100 times, and that of the gonads 3 to 4 times /338/. I^{131} emits β-particles and γ-quanta during its disintegration, making it possible to evaluate the activity during clinical studies of the γ *-radiation, which has a high penetrating capacity,* I^{132} *also emits* β *-particles* of medium energy 0.45 MeV (mega electron volt) and considerably stronger γ -quanta /312/

I^{131}, due to its suitable halflife, is extremely convenient for the study of the functional state of the thyroid gland and for experiments on metabolism.

The first reports on the use of radioiodine for the destruction of the thyroid gland were published in 1942 by Hamilton and Herz, Herz and Robertis (cit. from Klyachko,/78/). These reports were followed by a large number of works on radiothyroidectomy in various experimental animals as well as in patients with hyperfunction of the thyroid gland. Thus, radioactive iodine became one of the important methods used in order to act on the thyroid gland in experimental conditions and in therapy. The destructive action of radioactive iodine in the tissues is basically determined by its β-radiation. As is noted by V.K. Modestov /103/, total disintegration of one millicurie of radioactive iodine by β-radiation gives off 1,500 roentgens and by γ-radiation 130 roentgens.

The morphological and physiological effects of the action of large doses of *radioactive iodine were studied in detail* by many authors and the published material on this question was recently summarized in an article by Ya.M. Kabak and I.N. Tal'skaya /71/. This work, as well as the article by Ya. M. Kabak and M.M. Nikitina /67/, bring the results of studies on the action of large doses of radioiodine —I^{131}— on the thyroid gland of ducks and rats and on several

Chapter IX

THE METABOLISM OF IODINE AND OF THE THYROID HORMONES IN PATHOLOGY OF THE THYROID GLAND

(Metabolizm ioda i tireoidnykh gormonov pri patologii shchitovidnoi zhelezy)

As has been emphasized many times, one of the basic concepts of endocrinology is the recognition of the fact that in various pathological states the incretory gland may produce too much or too little of the hormonal products, but that it does not form other active compounds. This thesis evidently also applies to various forms of pathology of the thyroid gland. Isolated reports that have been published on the discovery of unusual iodinated proteins in the blood or on disorders of various stages in the process of hormone formation in some diseases of the thyroid gland do not contradict this concept, for the unusual proteins appearing in the blood of patients suffering from disorders of the thyroid gland do not have biological activity and defects in hormone formation also lead, in the end, to a reduction of the hormone secretion. But if in basic forms of thyroid pathology, such as endemic goiter, Basedow's disease, and myxedema we do not observe biochemical disorders in any stage of the chain of synthesis, or of secretion processes of the hormones, yet in some cases of thyroiditis, and particularly in cretinism, defects of hormone formation in the thyroid gland, or degradation of the iodinated components have been described.

In the basic forms of thyroid pathology the functional stage of the gland may be *augmented, reduced,* or *remain without any noticeable changes,* which may be discovered by the extent of absorption of radioactive iodine, by the clearance of iodine from the plasma, by the rate of hormone secretion, by the level of the plasma PBI, etc. Upon studying the tissue of a surgically removed thyroid gland of such patients, it is possible to discover changes of the total iodine content and of the iodinated organic components. Cases of hereditary cretinism lead to the discovery of defects in the hormone synthesis at one of the stages in the deiodination of diiodotyrosine and iodinated protein is found in the blood in cases of Hashimoto's disease.

In all forms of thyroid pathology evaluation of the functional state of the thyroid gland is made first of all. Formerly, the main criterion of this evaluation was the determination of basal metabolism. Upon studying the function of the thyroid gland with the use of radioactive iodine, it is possible to measure the various parts

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gland, as well as various criteria for the evaluation of its function.

A large enough number of works have been published on this question /103, 54, 155, 270/. Without elaborating on this question, we shall only limit ourselves to the exposition of some general theses. In a healthy man the accumulation of the

urine of patients receiving therapeutic doses of I^{131} at one time, or in portions. We also determined the iodine-containing components of the blood and urine by the radio-chromatographic method. The results of our studies show that the main part of the activity administered is accumulated in the thyroid gland within 24 hours and a high activity is noted in the blood during the same period, related to the presence of inorganic iodine. Activity bound to the protein gradually increases and is equal to about 80% of all the radioactivity in the blood after 48 hours. The main part of the iodine administered is excreted in urine within the first 48 hours, while in urine of thyrotoxic patients we find, apart from inorganic iodine, a whole series of other iodinated components, of which thyroxin is the main part. A detailed account of this work will be published in the future.

the I^{131} uptake by the thyroid gland and also in the level of the blood PBI, which is probably explained by the varying course of the disease.

In some diseases of the kidneys and the liver a low level of iodine is noted in the serum, combined with a state of severe hypoalbuminemia. But this is probably not related to a deficiency of the iodine carrier, for the restoration of the albumin concentration to its normal level by injecting pure albumin into the blood stream does not lead to an increase of the iodine concentration.

The metabolism of iodine in the tissue of the gland in various forms of goiter was studied in glands and nodules which were removed surgically This question shall be clarified further on, on the basis of the data from our laboratory.

In some forms of thyroid pathology, apart from the strengthening or the weakening of thyroid gland function, defects in one or another stage of the intrathyroidal synthesis of the thyroid gland hormones are observed. Such forms of biochemical pathology are combined with some manifestations of cretinism and are of a congenital character. In all cases a hypothyroid state sets in, in general, as a result of the elimination of any stage of the hormone synthesis

All the details of congenital defects in the process of hormone formation could be studied in detail, due to the use of radioactive iodine and of chromatographic studies of the iodinated compounds of the gland. The actual state of our knowledge on this question was presented in recent surveys of Mosier, Blizzard, Lawson /431/ and Clayton /242/.

An important contribution was made by Stanbury and his co-workers to the understanding of the nature of these organic defects in biochemical processes in the synthesis of the thyroid hormones. The following basic forms of these disorders have been described up to now.

1. The relative insufficiency of the transformation of inorganic iodine into an organically bound form. The first case of sporadic cretinism in which a metabolic defect was determined was described by Stanbury and Hedge in 1950 /539/. In these patients the absorption of iodine by the thyroid gland remains on a high level, but, in view of the absence of its binding into an organic form, iodine is easily ejected by administering thiocyanate. During this the thyroid gland contains practically no organic iodine, as is also observed upon blocking the gland with thiouracil. According to the opinion of a number of authors /396/, this defect depends on the absence of enzymatic oxidation of iodides into iodine.

2. The absence of dehalogenation in the thyroid gland. The first to report on this defect were Stanbury, Kassenaar, Meijer and Terpstra /540/ upon examining a patient with congenital goiter. Later, Stanbury et al. /543/, Hutchinson, Arneil, and McGirr /360/ studied such patients in detail and could determine that the capacity of the thyroid gland to take up iodine remains on a high level Organic binding of iodine also takes place, but the main mass of iodine remains in the form of iodinated tyrosines. This led to the conclusion that this form of congenital defect is related to the absence of the capacity to deiodinate diiodotyrosines, which in normal conditions easily separates iodine in the tissues, with return of the liberated haloid into the metabolic cycle. The case of goitrous cretinism recently described by McGirr /401/, having a hyperthyroid character of accumulating radioactive iodine, is possibly related to this group. It was shown that such a rare form of pathology of the thyroid gland, found in localities where there is no endemic goiter, is expressed by the hyperthyroid character of radioiodine absorption in the presence of goiter showing clear signs of cretinism. A similar case was described by V. P. Dyskin /56/. As was shown by the studies of McGirr, the iodine absorbed in these patients is included into the composition of organic compounds and forms iodinated

administered iodine in the thyroid gland begins immediately, it reaches 75% within 12 hours and almost 100% within 24 hours. The values of iodine absorption by the thyroid gland in a healthy man fluctuate widely, but they average 16-30%. During this time more than 60% of the administered dose is excreted in urine and about 10% is distributed in the whole body. In thyrotoxicosis the accumulation of iodine takes place more intensively and terminates more speedily, maximum absorption reaches up to 70% and more, but the greatest accumulation is noted after 8 hours, and it takes place very infrequently after 24 hours. Excretion in urine is reduced to low values. On the other hand, in hypothyroidism the thyroid gland captures a considerably smaller percentage of the administered iodine and effects this at a slower rate. The maximum inclusion in this case is 7-10% of the administered dose and is generally reached within 48 hours. A large part of the remaining iodine is excreted in the urine during the first 24 hours, but excretion goes on in smaller quantities for 1-2 days.

There is an inverse relationship between the extent of radioiodine absorption by the thyroid gland and its excretion in urine. This is why the excretion of administered radioactive iodine in the urine within 24-48 hours may also be a criterion of the functional state of the thyroid gland and the measurement of urinary clearance is one of the methods used in clinical conditions for the evaluation of the function of the gland /162/. Various formulas are used, expressing the simultaneous correlation of the I^{131} contents of the thyroid gland, the blood, and the urine /215/.

After absorption of a tracer dose iodide is speedily transformed in the thyroid gland into an organic form. The synthesized hormone is secreted into the circulation in the form of thyroid hormones and in the form of protein bound iodine in the plasma (PBI) The rate of appearance of considerable PBI quantities in the blood and its level depend on the functional state of the thyroid gland. This is why the determination of PBI of the plasma is one of the important tests for evaluating the activity of the gland. But determination of PBI is a complex procedure, demanding qualified analytic work, and cannot replace the generally accepted simple method of evaluating the functional state of the thyroid gland by the uptake of radioiodine. Values of the PBI in a healthy man and in a patient suffering from pathology of the thyroid gland fluctuate widely. Besides, there is a relatively large range in which the values of healthy and hyperthyroid subjects overlap. Astwood et al. /191/ obtained results for PBI of 0-32 μg%. The usual normal value is considered as being 5.8 μg%, with fluctuations from 4-8μg%. But values below 4 and above 15 μg% were also obtained.

In myxedema values above 4 μg% are infrequently obtained and it is a good indicator, permitting to distinguish between healthy people and those suffering from myxedema. Thus, 4 μg% may be accepted as the lower limit of the normal values.

In hyperthyroidism the level of the blood PBI fluctuates from 8μg to 23 μg per 100 ml of blood. But values lower than 8 μg% are also obtained. As is noted by Astwood, the level of PBI was lower than 8 μg in 3% of the hyperthyroid persons and in 18% of the euthyroid people it was above this value. This is why differentiation between hyperthyroid and healthy persons by the level of the PBI is not as reasonable as differentiation between myxedematous and healthy persons. Astwood thinks that 4.5 μg% correspond more to the upper limit of the PBI in the normal state.

According to the opinion of Staffurth and Birchall /538/, determination of PBI has great value in nontreated primary thyrotoxicosis. In other cases of thyrotoxicosis, its fluctuations do not reflect the real functional state of the gland.

In simple goiter, without manifestations of thyrotoxicosis, PBI is found within a normal range in 90% of the cases and it may be above or below 4-8 μg% in a small number of cases. In thyroiditis large variations are noted in the extent of

its bond in a pathologically-changed tissue. There were differences in the absorption of iodine,and in the creation of a considerable gradient and degree of binding with the protein, in sections of adenomatous tissues which were histologically identical. As is pointed out by the authors, these clear differences may be the expression of the changing state of the function of adenomatous tissue in the course of the disease. Studies on sections of carcinomatous tissue show that in cancer of the thyroid gland thiocyanate could not eject absorbed iodide even during blocking of the sections, but this iodide was not in an organically bound form.

Thus, the question of the presence of a special form of iodide in the thyroid gland, which cannot be ejected by thiocyanate in some thyroid disorders, was confirmed in this work.

The character of this form of iodine was studied in rats receiving propylthiouracil /458/. It was shown that iodide which cannot be ejected by perchlorate is found in a bound protein form, but this protein differs from thyroglobulin by the fact that it contains iodinated components mainly in the form of monoiodotyrosine.

Owen and McConahey /448/ reported the discovery of an unusual iodinated protein in the blood serum of patients suffering from thyroiditis. During electrophoresis of the serum proteins, after administration of tracer doses of I^{131}, noticeable amounts of radioactivity were found in the fraction precipitated with the proteins, but were not extractable by acid butanol. This component resembles thyroglobulin, but its real nature is not determined. During hydrolysis of the gland tissues, the authors could not note noticeable differences in the I^{131}-containing components, as compared [illegible] sections of Hashimoto's thyroiditis m[illegible]
thyroi[illegible]

PBI. In this form of thyroiditis a much larger quantity of unbound iodine is found in the tissues of the gland. Administration of thiocyanate considerably reduces the activity of the section. A similar picture is also observed in granulomatous thyroiditis, in which, according to the results of Owen and McConahey /448/, the thyroid gland cannot bind iodine organically.

Disorders of iodine metabolism in the thyroid gland have also been noted in cases of hypothyroidism provoked by the administration of iodine /449/. As reported by Morgans and Trotter /428/, hypothyroidism provoked by prolonged administration of iodine to euthyroid persons without thyroid pathology has at its root the loss of the capacity of the gland to synthesize organic iodine in the presence of an increased level of iodine in the plasma or in the thyroid gland.

Thus, besides quantitative changes in the degree of uptake by the thyroid gland, and the increase or the reduction of hormonally active compounds in the gland, there are clear disorders of the hormone formation processes in a series of cases of thyroid pathology.

There are but few reports on changes in the iodinated components of the thyroid gland, which are found in a free form as well as in the composition of thyroglobulins in various forms of disease of the thyroid gland. Trunell and Wade /584/ pointed to the abnormal fluctuations of the relative proportions of thyroxin and triiodothyronine in adenoma hydrolysates of two patients, but Stanley /545/ found that thyroglobulin from benign adenomas does not differ in chemical composition from the protein of a normal tissue.

The formation and metabolism of the thyroid hormones in various forms of thyroid gland pathology have recently been thoroughly studied in the Laboratory of Biochemistry of the Medical Institute of the krai of the Academy of Sciences of the

compounds similar to thyroxin. They are extracted by butanol, do not pass into alkaline fractions, are secreted into the blood just as iodothyronines, but the result of the studies showed that they have no biological activity. According to the results of Fletscher, Litvak, and Stanbury /299/, upon administering diiodotyrosine to such patients it remains in the organism for a longer time and is excreted in an unchanged form.

3. The defect in the condensation of iodinated tyrosine molecules into hormonally active molecules of iodothyronines. In these patients with hypothyroid goiter the uptake of iodine by the thyroid gland is also increased. The processes of tyrosine iodination and dehalogenation of mono- and diiodotyrosine are not disordered, but extremely small quantities of thyroxin are found in the gland and in the blood. This form of defect is characterized from the biological point of view, by the lessening of the condensation of iodinated tyrosines with formation of a thyronine ring, as a result of the absence of specific oxidizing enzymes.

There are also reports on other defects in the formation and metabolism of the thyroid hormones. Hutchinson, Arneil, and McGier /360/ described a case of infant cretinism which was not suppressed by treatment with dessicated thyroid gland, but was speedily cleared up with triiodothyronine. The authors assumed that in this case the defect depended on the absence of thyroxin deiodination, with formation of triiodothyronine. But the therapeutic effect of triiodothyronine, when there *is no amelioration by the use of thyroxin, was found only in one case* and the explanations brought forth are not well-founded. As is known, triiodothyronines are mainly formed in the organism not by deiodination of thyroxin, but by the condensation of mono- and diiodotyrosine molecules. As is correctly noted by Querido /465/, the concept of the absence of peripheral deiodination of thyroxin into triiodothyronine demands more direct proof. The low level of the blood PBI of these patients should be explained if thyroxin is secreted into the blood in sufficient quantities.

Clayton /242/ notes possible variations of the extent of enzymatic defects. It may be assumed that in simple goiter slight defects may take place in the synthesis of thyroxin, which could be compensated by the stimulation of the thyroid gland by TSH. He described *four children of one family* having euthyroid goiter, from whose thyroid gland iodine was speedily eliminated by thiocyanate. The author believes that, although these children have a defect in the organic binding of iodine, the extent of this defect is insufficient to bring on hypothyroidism when thyrotropic stimulation leads to hyperplasia.

Reports have been published on the appearance of an iodinated protein *differing* from thyroglobulin in the blood of a patient with congenital goiter. DeGroot *et al.* /257/ recently reported the discovery of an unusual protein in the blood of patients suffering from congenital goiter, containing in its composition iodotyrosines and *iodothyronines* combined into peptides. After hydrolysis, this protein gave monoiodotyrosines, diiodotyrosine, and thyroxin. But the hydrolysis was not total under the *action* [illegible]

the thyroid gland.

[illegible]

ed with an antithyroid substance, the *absorbed* I^{131} was not ejected upon adding thiocyanate. This shows possible *differences* in the form of iodide, or in the form of

1. The gland and the nodule take up radioiodine with different intensities, and this is clearly discovered upon determining the activity of thin sections. In thyrotoxic adenomata the nodule has a considerably higher activity than the gland, and in euthyroid goiter the main activity is found in the gland, which leads to a lower iodine content in the nodule

2. A relatively higher content of inorganic and of mono- and diiodotyrosine iodine is contained in the nodule than in the tissue of the gland, consequently, in these cases the increase of iodine absorption by the gland does not yet prove an increase in hormone formation. This result confirms our opinion that the thyronine ring is synthesized from mono- and diiodotyrosine molecules inside the cells; this is why the quantity of thyroxin in the tissue of the gland is always larger than in the nodule.

3. When there is colloid in the alveoli, a considerable part of the iodine in its composition is found in an inorganic form.

Upon comparing the activity of the free iodinated compounds, extracted from the gland without hydrolysis, to the activity of the compounds contained in the butanol extract of the tissue and gland hydrolysate, considerable differences are noted between the nodule and the tissue. Thus, for example, in a case of thyrotoxic adenoma the nodule had an activity of 25,000 disintegrations when β radiation was counted on sections weighing 10 mg and the tissue had 2,130 disintegrations, but a considerable part of the nodular activity was found in the form of inorganic iodine, while that of the tissue was in the form of iodinated amino acids

Thus, various interrelations are determined between the nodule and the tissue of the gland, which probably depend not only on the type of goiter but also on the periods of its development. The thorough study of the biochemical bonds, of the similarities and differences between the tissue of the gland and the nodule in various stages of hormone formation, may throw light on the problem of the interrelations between the gland and the pathologically changed tissue of the nodule, a problem which is as yet unclear.

Uzbek SSR, with the participation of workers of the Laboratories of Endemic Goiter and Pathohistology. After thorough clinical study and evaluation of the functional state of the thyroid gland by the uptake of radioiodine and by other criteria, patients waiting for operation received 100-200 μC of radioactive iodine and were operated upon 24 hours later. Apart from the generally accepted biochemical indicators, a thorough study was made on these patients of the iodinated compounds of the blood, urine, and the removed gland. In some of the patients the butanol extracts of the blood and urine were subjected to chromotography. The removed glands were subjected to histological studies, which were complemented in a series of cases by historadiographic studies.

The study of iodine métabolism in the thyroid gland was made separately in the gland tissue, in the nodule, and in the colloid in which total iodine, protein bound iodine, and inorganic iodine were analyzed by the usual chemical methods. The total activity of tissue sections, the activity of the protein fraction, and the free iodinated components extracted by butanol were determined by radiochemical studies. Chromatographic analysis was also made of the free iodinated amino acids, and of the butanol extract of the alkaline hydrolysates.

The total iodine content in various forms of goiter was studied in 30 glands which were surgically removed. In the presence of a nodule the determination of iodine was made separately in the tissue of the gland and in the nodule. Considerable fluctuations were found in the total iodine content and in the protein bound iodine in the gland and in the nodule, but it was not possible to determine a clear correlation between the type of goiter and the haloid content. It may be noted that in nodular goiter the tissue of the gland generally has a larger iodine content (from 16.5 to 95 mg %) and the nodule a smaller content (from 2.2 to 63 mg %). The lowest value for the total iodine content, and particularly for the protein bound iodine, is found in calcified thyroid glands with a very small colloid content.

The fractions of iodinated compounds were extracted from the homogenate of removed tissue by butanol before hydrolysis, and the material was then subjected to a 2N-alkaline hydrolysis The hydrolysate was also extracted with acid butanol. The extracts were studied by two methods 1) in order to determine the ratio of iodine, monoiodotyrosine, and diiodotyrosine to that of thyroxin, the extract was washed out with strong alkali and the activity in each part was determined separately; 2) in order to separate the various compounds more precisely, the butanol extracts were subjected to chromatography in several solvent systems. We obtained the best separation in a system of butanol-dioxane-ammonia (4 1:3). Results obtained by analyzing the tissue of the gland and of the nodule show that 24 hours after the administration of I^{131} the main mass of iodine in the gland is found in an organically bound form. Only 1-4 % of the total activity is accounted for by inor- [illegible] ...entage is consider- [illegible] the inorganic io- [illegible] ...ion of mono- and diiodotyrosines passing from the butanol extract into the alkaline solution is 40-70 % and the thyroxin fraction is 20-40 % of the total activity. During analysis of the nodular iodine compounds the fraction of mono- and diiodotyrosines is 45-83% [illegible] Especially low values of thyroxin and correspond- [illegible] and diiodotyrosine iodine were obtained [illegible] ...sions. Thus, in one case of a grade IV [illegible] the total activity, the fraction of mono- and diiodotyrosine contained 64.[illegible] %, and thyroxin contained only 7.1 % of the total activity.

Thus, the results of the studies made by us show definite differences in respect to the various fractions of the iodinated compounds in the tissues of the gland and the nodule. These differences are as follows

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CONCLUSION

The new stage in the studies on the formation and metabolism of the thyroid hormones, beginning with the use of radioactive iodine and the chromatographic method, led to the successful solution of many fundamental questions of the biochemistry of the thyroid gland hormones. But the completion of the study on some aspects of the problems raise new problems, whose solution may be considered as being probable, in view of the results which have already been obtained. Researchers in this domain of biochemistry have many important problems before them, whose solution should lead, on the one hand, to the clarification of the complicated processes of intracellular metabolism, and on the other hand, to that of neurohumoral mechanisms, regulating with surprising precision the production, distribution, and action of the hormones in the organism as a whole. The determinations of the nature of the form of thyroxin acting at the cellular level, the thyroid hormone mechanism of action, the particularities of their metabolism in the various regions of the central nervous system, and of the biochemical basis regulating the formation and secretion of the active elements of the gland, apart from being interesting from the theoretical point of view, are undoubtedly a problem of paramount practical importance in medicine. These objects were concisely formulated by E.A. Vasyukova in the following manner: "It is necessary to expand, in every possible way, the work in the field of hormone metabolism as well as on the methods of their inclusion in the biodynamics of the effector organs, to bring out clearly the role of the hormones in nervous trophism and the role of the hormonal link in the neuroreflectory reactions" /25/.

The solution of these questions demands persistent research, as well as carrying out of extensive studies, using the possibilities of modern methods.

Upon taking up the writing of this monograph, we attempted to sum up the achievements reached in the study of the thyroid hormone biochemistry during the last decade and to attract the reader's attention to works in this domain, thus promoting the development of new research.

Successful research on such important questions as the modern biochemistry of hormones, as well as the study of their tissue metabolism, their mechanism of action, and their physiological effect, requires well-equipped laboratories, pure preparations, compounds labeled in various positions, and a wide experimental basis. These conditions are often difficult to obtain, especially for researchers working far from the large urban centers. But we hope that the existing shortcomings, which have been to a considerable extent the cause for the lag in biochemical research, shall be corrected in the near future. Guarantees for this is the daily attention paid by the Communist Party to the development of science in our country, as well as the strong interest shown by the XXIst Congress of the Communist Party of the Soviet Union in the further development of biology, and in particular of biochemistry and biophysics.

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